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TAPE RECORDINGS OF THE ELECTROCARDIOGRAM IN NEWBORN INFANTS

BY ILKKA VÄLIMÄKI

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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From the Cardiorespiratory Research Unit, the Department of Physiology and the Children's Hospital of the University of Turku Turku, Finland

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Vammala 1969, Vammalan Kirjapaino Oy

CONTENTS

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INTRODUCTION

At birth a haemodynamic revolution occurs in the circulation. A series of integrated events follow each other within a couple of minutes: the aeration of the lungs is accompanied by the inception of functional pulmonary circulation, the placental circulation ceases and the ventricles of the foetal heart, coupled in parallel, are reconnected in series by means of the closure of the foetal circulatory shunts, the foramen ovale and the ductus arteriosus. These perinatal cardio-pulmonary adjustments are the largest of the entire human life. A delay or inco-ordination of this transformation may have serious consequences. The magnitudes of both depolarization and repolarization deflections of the electrocardiogram, are proportional to the myocardial muscle mass, and reflect cardiac cell metabolism. Thus, information about the adaptation of the heart to the haemodynamic changes can be obtained from the electrocardiogram.

In obstetric departments and neonatal wards there is a tendency towards more and more intensive observation and therapy of newborn infants. The important primary functions, respiration and heart action, are to be continuously monitored. It is thus essential for correct diagnosis to know the limits of the normal variation of these functions, and also features typical of pathological conditions. This presumes the use of long term recordings in research work.

Continuous electrocardiographic and heart rate recordings, without affecting the activities of the subject, are produced in two main ways: 1. using a miniature electrocardiographic transmitter attached to the patient, and a special receiver for detection and reproduction of the signal (radiotelemetric instruments), or 2. employing a small portable electrocardiographic tape recorder connected directly to the patient. A third method, applicable also to these two apparatures, is to conduct the electrocardiographic signal directly to a computer where the information can be processed automatically, but this can scarcely be realized in most hospitals at the present time.

The purposes of the present investigation are: to define a suitable and interference-free electrocardiographic tape recording technique for small infants; to study peculiarities in the signal reproduction of tape recording equipment, and to determine the alteration of the heart rate and the electrocardiographic signal postnatally in full term and premature infants, with long period recordings beginning on the first day of life.

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CONVENTIONAL ELECTROCARDIOGRAPHY IN NEWBORN INFANTS

Full term newborn infant

Paediatric electrocardiography was started by the investigation of Nicolai & Funaro [61] in which a deep S_I *deflection, different from the S wave* of adults, was found to be a distinctive electrocardiographic feature of small infants. Thereafter an enormous number of studies have been performed the character of which has followed the evolution of electrocardiographic techniques and of modern views of human haemodynamics. The electrocardiographic peculiarities of childhood have been designated as a function of age. The transformation of these features appears to be rapid in early infancy particularly during the neonatal period As a result of this, the ECG of the newly born cannot be compared with that recorded days, weeks or months after birth.

*Neonatal electrocardiographic find*ings were described in such publications as Hecht [34] Smith [83] Burghard & Wunnerlich [8] two detailed articles of Nadrai [59 60] that of Battro *& Mendy* [5] *Schaffer* et al. [78] Tudbury & Atkinson [92] and Alimurung et al. [2] In the light of these investigations and the monograph »Electrocardiographic Studies in Normal Infants and Children by Ziegler [112] it was possible to define the typical features of the neonatal ECG *as follows*

1 The mean heart rate was 120 to 130 beats per minute ranging from 90 to 200 beats per minute

2 The neonatal P waves were found *higher than those of older children*, and the duration of the P wave became longer after the neonatal period. Nadrai showed that the P R interval was prolonged in newborn infants [60]

3 The *ventricular depolarization* complex indicated right ventricular preponderance, which later in childhood gradually turned into the left ventricular dominance peculiar to adults. A prominent Q wave was often detected in standard leads II and III and left precordial leads.

4 *Inverted T waves* were quite common in the precordial electrocardiogram without any evidence of myocardial disease Also a small S-T deviation up to 0.2 mV was often established *in chest leads*.

In the investigations published after 1950 contradictory reports concerning neonatal *T wave* alterations were checked. Both Ziegler [112] and Furman & Halloran [23] divided the neonatal period into smaller segments. In this way it proved possible to clarify ventricular *repolarization during the* first hours, first days and weeks after

birth. According to these later observations the T wave was at first mostly positive in the right precordial chest leads, later becoming inverted [14, 16, 30 72, 84, 86, 107] On the other hand, left precordial T waves were negative immediately after birth and became positive later on. Schaffer et al. noted that the T wave was negative on the right, and positive on the left precordium [78] Also Furman & Halloran detected inverted T_{V1} in more than 50 per cent of newborn infants, there were no negative left precordial T waves in this series [23]. Sodi-Pallares et al. paid attention to the convex S-T segment, and peaked, asymmetric T wave, peculiar to the neonatal right precordial electrocardiogram [84] Stern & Lind found that the inversion of T_{V1} occurs between the ages of 30 minutes and 6 days [86] This was confirmed by DePasquale & Burch [17] Scott & Franklin reported that the T wave inversion in the right chest leads occurred during the first week of life [80] Hait & Gasul showed that the axis of the T wave initially for 0—5 minutes post partum, pointed to the left, then shifted to the right at the age of 1—6 hours, and then once again to the left in a time of seven days. This variation was suspected to be a sign of transient physiologic left ventricular strain [32]

The comparison of electrocardiographic findings with neonatal haemodynamic observations offered new possibilities for explaining T wave alterations. Dupuis et al. demonstrated that changes of T_{V1} coincided with the disappearance of pulmonary hypertension [19] Emmanouilides et al. established a correlation between positive right precordial T waves, high P waves and pulmonary hypertension. There was also a positive correlation between the negative T_{V6} deflections and a neonatal left-to-right shunt in ductus arteriosus. R/S ratio in the V6 lead was found to be less than one in cases where the pulmonary arterial pressure was low in relation to the systemic arterial blood pressure [20]

The U deflection was rather rare in the electrocardiogram of newborn infants. Michaëlsson found U waves up to 0.2 mV of magnitude in about one third of infants at the age of one week or less [54]. This observation was confirmed by Walsh [107]

The monograph of Wasserburger gave data about normal and abnormal QRS complex morphology in unipolar leads during childhood. This material included a group of 60 infants 0—2 months old, 30 of whom were under 1 week old. Rs and rsR' patterns were mostly discovered in the right chest leads and qRs pattern, with a tendency to low voltage and clockwise rotation, was a typical finding of left precordial ECG [110]

Interracial differences in neonatal ECG were described by Sutin & Schrire [90] Right ventricular preponderance was reported as more prominent in white infants than in South African coloured and Bantu infants.

According to the literature, there seems to be much variation in the values of different conduction phases of neonatal electric cardiac activation. The duration of the P wave ranged from 0.02 to 0.10 s [23 24, 54, 69 102, 106, 112] the P-R time was 0.06—0.14 s [23, 60 72, 102, 106, 112] and the QRS interval 0.04—0.06 s [23, 24, 54, 60 69 72, 103, 112] The measurements of these intervals were generally performed in standard lead II. DePasquale & Burch stated that the duration of P

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deflection was constant in the neonatal period [17] The results of Ziegler [112] Walsh [102] and Jagielski et al. [39] indicated a shortening of the P wave duration after birth. The heart rate had no effect on the duration of atrial depolarization. Generally shorter P R intervals appear with higher heart rates, but in newborn infants this phenomenon is less marked [3] Kessel found that the P-R interval was longest 3—5 hours after birth, regardless of heart rate [42] Also in the series of Michaëlsson, the maximal P R intervals were noted during the first day of life [54] A gradual decrease of the P R interval in the neonatal period was a common finding [17 39 12, 106] The minimum interval was reached in 1—7 days [112]

The duration of the ventricular depolarization complex was minimal during the first 4 weeks of life [23 112] DePasquale & Burch [17] Walsh [103] and Jagielski et al. [39] establish ed the decrease of the QRS duration in their newborn materials. The materials of Nadrai [60] Ziegler [112] Michaëlsson [54] DePasquale & Burch [17] Walsh [103] and Jagielski et al. [39] indicated a transitory prolonga tion of the Q-T interval after birth Walsh demonstrated that the prolongation of the Q-T interval was mainly due to the prolongation of the duration of the S-T segment [103]

An extreme variation exists between different investigations in respect to the frequency of cardiac rhythm and conduction disturbances during the neonatal period. A common characteristic of all these disturbances, however is that they are asymptomatic. Some investigators have not mentioned any arrhythmias, although quite large ma terials have been examined. The possi bility of the appearance of a sudden arrhythmia in a short recording is rath er small and, on the other hand, mild sinus arrhythmias would not be clas sifield as true arrhythmias by all authors.

The most frequent arrhythmia in newborn infants seems to be the sinus arrhythmia [16 23 30 54 59 60 68 92, 112] The highest incidence of respiratory arrythmias (42 %) was reported by Nadrai [59] There are regularly more sinus arrhythmias to be detected in association with lower heart rates [112] In most investigations there were only sporadic cases of extrasystole [19 23 54 59 60 72, 83 92] although authors found premature beats in as much as 30 per cent of their material [8] Ventricular extra systoles proved to be more common than supraventricular ones.

Single cases of auricular flutter [112] wandering pacemaker [23, 72, 104] Wolff Parkinson-White syndrome [104] nodal rhythm [19] sinus arrest and supraventricular arrhythmias [54] were discovered in newborn materials. Most of the arrhythmias occurred on the second and third day of life [54] Ziegler described an infant with a grave transitory ventricular conduc tion disturbance [112] Both Schaffer et al. [78] and Walsh [104] found one case of right bundle branch block in their materials. There was also one case with a ventricular conduction disturbance in the material of Stern & Lind, which normalized during the observation time [85]

In an impedance pneumographic and electrocardiographic study we found sinus arrhythmia in 60 per cent of the material of 50 newborn infants at ages of up to 10 days. Half of the sinus arrhythmias appared to be connected

with periodical respiration. Although the recording time was very much longer than in ordinary ECG examination, no other arrhythmias were detected [15].

Heart arrythmias in childhood was the theme of the monograph of Landtman [45]. No special attention was paid to the neonatal period, but it was mentioned that sinus arrythmia was found, although less pronounced, in the youngest age groups too. Premature beats, auricular flutter and fibrillation, seldom appeared in infants. Two cases of paroxysmal tachycardia, typically occurring in infancy were detected in the neonatal period. Conduction disturbances were also quite rare, only one newborn infant with a complete A V block being described.

Premature newborn infant

According to the early investigations of Noeggerath [82] Hecht [34] Burghard & Wunnerlich [8] Londe [49] Raiha [67], and Nadrai [59 60] it could be concluded that there is no neonatal electrocardiogram peculiar to premature babies, although some features differ from that of full term newborn infants.

— low voltage in QRS complex was more common in premature material, especially in the group with a small birth weight,

— P and T waves were also of lower amplitude and could even be lacking,

— the premature generally had higher heart rates,

— less respiratory sinus arrythmia was found among prematures, but real rhythm irregularities were quite frequent [67].

A contrary result was expressed by Landtman, where many arrythmias, though not sinus arrythmia, were rarely found in premature infants [45]. The reason for this discrepancy may be the longer ECG recording time employed by Räihä [67].

More information about the ECG of the premature newborn infants was obtained using precordial leads [38, 47 74, 75, 76, 87 101]. Less prominent right axis deviation was found in premature babies than in full-term material, and deep Q waves were common in the left precordial leads. The right precordial T waves appeared to be *often negative during the first day of* life, which was believed to be a sign of a less marked right ventricular strain than in infants delivered at term. It was suggested by Stoermer that the persistence of positive right precordial T waves indicated abnormal right ventricular hypertrophy [87]. A shift of the negative T wave to the left was a common finding in the series of Thaon [91] Stoermer [87] and Salmi et al. [76] The left precordial T waves were mostly positive during the first day the same was the case after the second day of life. Thus the behaviour of neonatal T deflections in the left precordial ECG in premature infants resempled that of full-term babies. The P R interval was a little shorter in the premature compared with the values of the full-term neonates, but also prolonged atrio-ventricular conduction was to be detected *[74, 75, 91]*. The prematures had QRS intervals of the same, or smaller magnitude as the full-term infants [75, 87 91].

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that differing electrode placements produced very similar patterns in both chest leads studied, and thus the bipolar lead C5R-C5 was accepted for continuous recording. The oscilloscopic presentation in AVSEP differed from the pattern produced with the conventional machine. These differences included deeper S waves, slight deviations of S-T segment and deformations of T wave (socalled »pre-T notch» and »post T dip»). Basic electrocardiographic patterns of healthy adults were presented. The P wave and QRS complex were found to be quite stable, whereas the S-T T segment showed both dynamic and individual variations. Some features of the most common arrhythmias were presented, and difficulties in their identification were discussed. Stress was also laid on the importance of experience in excluding artifacts produced by the system itself.

Both Norland & Semler [63] and Corday et al. [13] used Holter's instruments to examine a large number of patients, mainly adults, among whom they picked up case reports concerning evanescent cardiac arrhythmias and stenocardiac attacks. Descriptions of the use of the tape recording method including case reports were published also by Arstila et al. [4] Roskamm et al. [71] Matzdorff & Schmidt [52], and Shumak & Brown [81]. Gilson et al. [28] described 4 cases with unusual QRS alterations among a material of 400 recordings. Gilson [25] published a longitudinal study of AVSEP patterns recorded in adult men during four years. It was found that a similar basic pattern was recorded every year in 81 per cent of the cases. Alterations were detected mostly in repolarization deflections. Arrhythmias were surprisingly rare. Sanders & Martt [77] reported observations of the use of electrocardiocording at high altitude.

The advantages and limitations of Holter's method were discussed on the basis of carefully standardized recordings performed in a large group of active adult men [35]. The characteristics of several Electrocardiocorders of different type series were compared. The speed constancy and cumulative timing error of the new Model 350 C series were found to be better than those of the older Model 350 C. Also a small time non-linearity in the scanner time-base was detected. A marked decay at the end of a test square wave was observed both in the scanner and charter outputs. The final ECG writer of the charter was not responsible for this phenomenon. The over-all frequency response was confirmed to be practically equal with that specified by the manufacturer. These results indicated that some distortion, especially in the low frequency components, i.e. S—T—T region, of the ECG is to be expected. This fact was also confirmed by studying the configuration of an ECG test signal. There were often difficulties in identifying S—T deviations and arrhythmias with the scanning technique. It was concluded that the interpretation of changes particularly affected by the electronic peculiarities of the instruments, e.g. S—T deviations and T wave abnormalities, can lead to false results, when the limitations of the method are not understood. For a more accurate analysis of recordings a photographic write-out of R—R intervals with real-time scanning, and a careful examination of all potential segments of abnormality was recommended.

Short case reports of arrhythmias, e.g. conversion of paroxysmal tachycardias

of heart rate was 100—200/min. The mean heart rate was higher than in full term infants. One case with an abnormal bradycardia of 65 beats per minute was mentioned. Premature babies with a birth weight less than 1500 g tended to have faster heart rates, especially at the age of one to three months. Arrhytmias were quite uncom mon in this series. The P wave dura tion, P R interval, and QRS interval increased during the first year of life. The Q-T index had a minimum at one to three months. The right precordial P waves were often peaked or diphasic during the first week of life. This phenomenon had been observed earlier and was suspected to represent a sign of right atrial overload [76 91 101 111] 75 % of the material had a right axis deviation, and 6 % had a left axis deviation at birth [105] T deflections were well defined but low in the chest leads, while the observations concerning the direction of T waves were in argeement with earlier investiga tions. U waves were discovered in about one third of the material at some time during the period observed. They were mostly found in the right precor dial ECG

Peaked P waves and a low QRS voltage were also reported by Fonseca Costa et al. [22] These authors found a relationship between the greater occurrence of Q_{V6}, negative right precordial T waves, and lower birth weight. This was considered to be a sign of a greater degree of immaturity The higher P waves shorter intervals of cardiac activation, and lower voltage of the ECG of premature infants were confirmed by Berlinerblau [7] and it could be concluded that no clear electrocardiographic signs typical of premature infants could be defined.

CONTINUOUS ELECTROCARDIOGRAPHY

Conventional electrocardiographs have some disadvantages for special purposes. Long-term recordings are un comfortable for the subject, because he is connected to the instrument and thus unable to perform normal activities. On the other hand these cardiac changes during every-day work are the most important criteria for the diagnosis and the degree of invalidity of a spesific heart disease. Another problem is the adequate analysis of a long period segment of electrocardiogram consisting of thousands of signals with almost equal configuration. The length of a roll of a conventional electrocardiograph paper is also a limit for record ings lasting hours or days.

All the problems mentioned above were resolved technically by a small portable electrocardiographic tape recorder (Electrocardiocorder) and the rapid analysing equipment (AVSEP Audio-Visual Superimposed Electrocar diographic Presentation) of Holter in 1961 [36] These instruments, manu factured commercially by Avionics Research Products Corporation, Los Angeles, California, will be described more thoroughly in section I of this investigation.

Observations concerning the clinical use of Holter's tape recording system were published by Gilson et al. [27] Attention was paid to reducing the inaccuracy of the recording by improv ing recording technique. Comparisons were made between the electrocardiographic configuration in unipolar and bipolar chest leads, and also between the fidelity characteristics of a conventional electrocardiograph and those of Holter's instruments. It was concluded

that differing electrode placements produced very similar patterns in both chest leads studied, and thus the bipolar lead C5R-C5 was accepted for continuous recording. The oscilloscopic presentation in AVSEP differed from the pattern produced with the conventional machine These differences included deeper S waves, slight deviations of S-T segment and deformations of T wave (socalled pre-T notch» and post T dip»). Basic electrocardiographic patterns of healthy adults were presented. The P wave and QRS complex were found to be quite stable, whereas the S-T T segment showed both dynamic and individual variations. Some features of the most common arrhythmias were presented, and difficulties in their identification were discussed. Stress was also laid on the importance of experience in excluding artifacts produced by the system itself.

Both Norland & Semler [69] and Corday et al. [13] used Holter's instruments to examine a large number of patients, mainly adults, among whom they picked up case reports concerning evanescent cardiac arrhythmias and stenocardiac attacks. Descriptions of the use of the tape recording method including case reports were published also by Aratila et al. [4] Roskamm et al. [71] Matzdorff & Schmidt [52] and Shumak & Brown [81] Gilson et al. [28] described 4 cases with unusual QRS alterations among a material of 400 recordings. Gilson [25] published a longitudinal study of AVSEP patterns recorded in adult men during four years. It was found that a similar basic pattern was recorded every year in 61 per cent of the cases. Alterations were detected mostly in repolarization deflections. Arrhythmias were surprisingly rare. Sanders & Martt [77] reported observations of the use of electrocardiocording at high altitude.

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to sinus rhythm, A V blocks of different degrees, and ectopic pacemakers in childhood studied with Holter's appa rature were published by Morgan et al. [56] and Välimäki [96] The former investigation included an example of processing the tape through a computer to obtain a *histogram* of R—R intervals.

CONTINUOUS ELECTROCARDIOGRAPHY IN NEWBORN INFANTS

In 1965 Morgan and Guntheroth published data obtained from 50 newborn infants at the age of one hour to 7 days by means of Holter's apparature [57] Standard lead I was used and recordings were taken for 3 1/2 to 5 hours Primary attention was directed to the cardiac rhythm. Sinus arrhythmia was observed in all infants The heart rate varied from 70 to 180 per minute Occasional premature beats were found in a few infants. One case of incomplete atrioventricular block was also mentioned Thus quite a normal cardiac mechanism was usually found in full term babies.

The case was otherwise with premature newborn infants, according to the earlier report of Morgan et al. [55] The series consisted of 20 infants at ages from 5 hours to 29 days. A marked sinus bradycardia was observed in 8 cases and 5 additional infants had sinus bradycardia with nodal escape One infant had a first degree A V block Sinus bradycardia was more common in the lower birth weight groups. The effect of digitalization and the vegetative tonus of premature infants were discussed on the basis of these results.

Our team also introduced two case reports of newborn babies, one with vegetative T wave changes after crying and the other with 2 1 A V block which was transformed first to sinus rhythm, then to a bizarre ventricular conduction pattern and later once again to sinus rhythm with S—T deviation [4] Preliminary reports of the present investigation were published in abstract form [95 97]

PRESENT INVESTIGATION

SECTION I DEVELOPMENT OF METHODOLOGY

THE EQUIPMENT OF HOLTER-AVIONICS

The frequency components of human electrocardiographic signals include too low frequencies to be directly utilized in electronic apparatuses. Thus a higher frequency carrier wave, modified (frequency modulated) by the cardiogenic signal, is employed in units that allow long segments of ECG to be recorded on a magnetic tape. For this procedure, large, complicated, and expensive devices are required.

Full freedom in transportability of the recorder and relative simplicity of the analyser unit were gained, at the same time avoiding the frequency modulation, in the electrocardiographic tape recording method introduced by Holter [16]. The apparature of this method consists of small, battery-powered recorder (Electrocardiocorder ®), a rapid analyser (Electrocardioscanner ®), and a writer unit (Electrocardiocharter TM).

Electrocardiocorder

Electrocardiocorder Model 350 is miniature twochannel recorder weighing 1350 g, designed to be carried by the subject. The tape speed is exceptionally slow only 0,31 cm/s. The frequency response of the machine is 0,1—100 cps. The ECG signal is simultaneously recorded on two tracks of the tape by the two channels of the device. One is the actual ECG pattern channel by which the ECG is amplified, and, mixed with a bias alternating current, recorded on the tape in the pattern recording head. The other is a trigger channel by which the ECG pulse is transformed into a sharp trigger pulse. The trigger head is located at some distance from the pattern head, which enables slightly earlier recording of the trigger signal on the tape. The purpose of this arrangement is that the trigger signal will trigger the sweep of the »pattern» display of the Electrocardioscanner and the QRS complex of the synchronous pattern recording will be placed in the middle of the sweep. Small reels of magnetic tape provide a recording of 5 to 15 hours, depending on the thickness of the tape. The capacity of the power supply a small nickelcadmium battery restricts the continuous recording time to 10 hours. The original electrodes and cords are for bipolar leads. A marking and calibration deflection of 1 mV may be recorded on the tape by pushing calibration button in the operating panel of the Electrocardiocorder. A repetitive one-millivolt pulse, with a frequency of 1 cps, can be obtained by means of the One-Milli volt Calibrator (Avionics) in order to calibrate the scanner unit.

Electrocardioscanner

The recording is analysed at a 60 times accelerated tape speed in the Electrocardioscanner Model 450. Thus band width of 6—6000 cps is reached, and the ECG potentials can be reproduced without frequency modulation. The accelerated play back technique also enables the rapid analysis of a long recording. The ECG pattern signal is applied through an amplifier to the ECG-pattern» oscilloscope (AVSEP») of the scanner. The trigger signal is utilized to adjust the length of the sweep of the oscilloscope equal with the R—R interval. This produces a superimposed presentation of successive ECG complexes on the screen.

Thus sudden changes in the ECG are easily detected as a movielike alteration of the PQRST *configuration.*

A saw tooth voltage, proportioned to the recorded R—R intervals, is fed to the other oscilloscope (Arrhythmiagraph) of the scanner unit to indicate the variation of the heart rate, which is also to be heard as a steady growl through a loud speak er This AVSEP technique enables the *examiner to concentrate* on *following the* ECG pattern on the screen, while the heart rate can be heard at the same time. Phenomena recorded on the tape can be timed by comparing the diary notes of the *Electrocardiocorder* examination and the time reading in a small clock of the scanner which is mechanically turned by the tape. Both oscilloscopes are to be calibrated in dependently with the one-millivolt rectangular *pulse. This pulse is a reference* for both voltage and timebase calibration.

Electrocardiocharter

If electrocardiographic abnormalities are detected during the play back procedure in the scanner these can be written out by means of the third unit, Electrocardiocharter Model 550 The original recording is placed on the operating deck of the machine, where the tape speed is once again the original 0.31 cm/s. The movement of the recording can be followed with a real time clock similar to that of the scanner *Because of the slow tape speed, the gap* of the reproducing head of the charter must be unusually wide to detect the slowly changing magnetic field. The signal is amplifield and fed to the input of an oscillograph (Burdick EK III Electrocardiograph), to be printed on a conventional ECG paper

The operation demands *(small size,* porta bility signal reproduction of good quality simple construction) of the Electrocardiocorder AVSEP instruments have led to some technical compromises in the manufacturing *of these devices.* The stability of the baseline is achieved by restricting the low frequency response, which leads to some insufficiency in repeating some essential frequency components of the ECG It has been stressed that findings obtained with this method are not comparable to those of conventional electrocardiography [27 35] *Although* a considerable non-linearity of the frequency response already exists in the recorder stage, additional distortion is evidently produced by the charter procedure. To avoid these distortions an addi *tional method has been developed for* printing the recorded tape information on ECG paper

MV 1 METHOD

This method was designed *for* a cardiological laboratory in which there is regular ECG equipment, e.g. electrocardiographs and oscilloscopes available, and thus only two additional components, a tape recorder of high quality and a special FM-modulator demodulator MV 1, are needed. This last has been developed and tested in the *electronic laboratory of Lääketukku Oy* Helsinki, Finland, and in the Cardiorespira tory Research Unit of the University of Turku. The MV 1 unit itself was constructed by an engineer T Ahman (Lääketukku Oy) Preliminary reports concerning this method have been published previously [50 113]

According to this method, the original Electrocardiocorder recording is analysed in the Electrocardioscanner and during the play back procedure the ECG signal is taken from the ECG output of the scanner to the MV 1 unit. *In this unit* the signal is frequency modulated and amplified, and then transferred for a re-recording to a regular high fidelity tape recorder *For this* purpose we have used an Akai M-8 tape recorder (Akai Electric Co. Ltd., Tokyo), which has the frequency response of 30—25 000 cps. The tape speed of the re*recording is 38,1 cm/s.* After the diagnostic portion of the original recording has been re-recorded, the re-recording is played at the tape speed of 4,76 cm/s and the signal is fed back to the MV 1 where it is amplified and demodulated and transferred to a conventional electrocardiograph (Mingograph 34 Elema, Stockholm) to be *printed* on paper The whole of this procedure is essential, because normal oscillographs are not able to write all the fre-

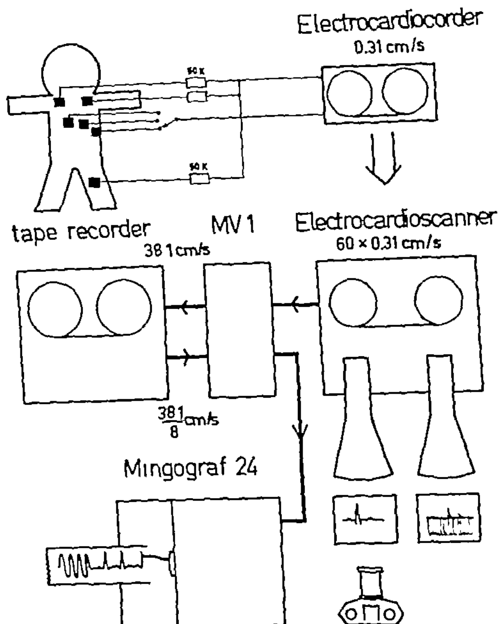


Fig 1 Block diagram of the tape recording and analysing procedures of ECG with Electrocardiocorder and Electrocardioscanner — MV 1 — Akai M-8 tape recorder — Mingograf 24 chain.

quencies of 6—60 000 cps produced by the Electrocardioscanner. As the tape speed of re-recording is reduced to 1/8, frequency range of 0.75—750 cps is reached. Most rapid oscillographs are ble to repeat these frequencies without a noteworthy non-linearity. The frequency modulation enables better signal reproduction, in fact there are no restrictions with regard to the representation of lower frequencies. An additional oscilloscope is connected to the DC-amplifier of the Mingograph. Thus the ECG pattern of the re-recording is visualised, and the heart rate is to be heard in

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recording for hours or days, mostly without oscilloscope control, and when we should like to get electrocardiographic information even during irritation, crying, and movements.

In the present investigation, the occurrence of the local alternating currents in the rooms of hospital wards was determined by utilizing a special antenna loop connected to an electrocardiograph. The place with a minimal inducting alternating current was chosen for recording. A Faraday cage was placed on the bed or incubator of the infant. The connecting wires, of minimal length, were supplied with a metal mantle outside the Faraday cage. The cage, bed, mantle, and the case of the recorder were earthed with a single wire. Earthing of the patient was not needed.

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The proper attachment of the electrodes is essential to minimizing the base line movement, and producing an electrode-skin resistance suitably low for equipment applied. Various standard electrodes and electrode jellies were tried. Finally our own miniature electrodes were constructed, which consisted of a 1.2 × 1.2 cm brass net screen connected to the wire by means of a snap fastener. Since the wire had to be exceedingly flexible, it was made of a hearing aid wire in which the conducting metal tape was wrapped around a cotton. The best electrode jelly proved to be Trucon Electrode Paste (Electrodyne Westwood, Massachusetts). The skin was cleaned with alcohol solution, rubbed until a mild erythema appeared, and the electrode, provided with jelly was attached to it with 3M N:o 1525 Blenderm Tape. Both the jelly and the adhesive tape were well tolerated during a period of 20—30 hours.

Three chest leads, V1, V3 and V5 were recorded successively. These leads were chosen not only because of the high signal-to-noise ratio, but also because there is a lot of information about results obtained with chest leads by conventional electrocardiography. This enables conclusions concerning the position of the cardiac electric axis to be drawn from results recorded with these three leads, and finally because the lead system is not too difficult to attach quickly. Resistors of 50 kΩ were connected in the classical manner to the central terminal. A lead selector constructed in our laboratory made the changing of leads possible.

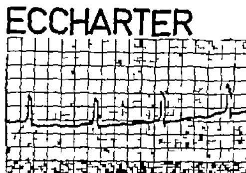
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the loudspeaker of the Akai tape recorder Once again an audio-visual presentation is utilised, and *this facilitates* the detection of momentary alterations of the recorded ECG For this oscilloscopic display the Atlas 46 A oscilloscope (Atlas-Werke A. G *Bremen) has* been used.

The block diagram of the electrocardi ocording and analysing procedures is presented in Fig. 1. The recordings of one-millivolt rectangular calibration pulse made with Mingograph 24 and the Electrocardiocorder the latter recording written out by means of the Electrocardiocharter and the MV 1 link, are compared in Fig. 2. We have tested the responses of both the scanner unit and the MV 1 link, by making an Electrocardiocorder recording with a sine wave pulse generator The voltage losses detected in the middle of the frequency range of the scanner ECG output being compensated in the construction of MV 1 amplifier

In practice, the Electrocardiocharter is throublesome to use, because the original recording must be removed from the deck of the scanner to that of the charter and the interesting point of the recording can thus be lost. The detecting of such a point can be difficult without an oscilloscope control, and involves the expense of much time and ECG paper In the MV 1 system the final signal can be continuously followed with an oscilloscope and a loudspeaker and only the essential segments need to be printed on paper The original recording can stay on the scanner deck all the time These practical difficulties have been par tially eliminated in the Composite Electrocardioscanner Model 651 of Avionics, which includes both the scanner and the charter units.





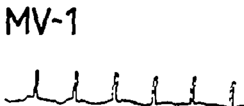




Fig. 2. Mingograf 24 Electrocardiocharter MV 1 and Electrocardioscanner reproductions of the 1 mV/1 cps calibration pulse of One-Millivolt Calibrator

ADJUSTMENTS OF THE APPARA TURE FOR THE PRESENT STUDY

Recording

The AVSEP-scanner analysis presumes an undisturbed tape recording *of* the ECG signal. Three major disturbing factors must be eliminated 1) the alternatig current noise 2) the muscle potentials and 3) the wandering of the base line These *factors become* particularly important when we have an unco-operative subject like a new born infant, when we must continue our

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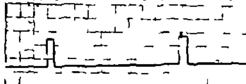
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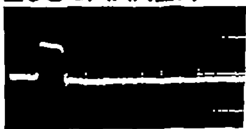


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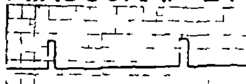
Three chest leads, V1 V3 and V5 were recorded successively These leads were chosen not only because of the high signal to-noise ratio, but also because there is a lot of information about results obtained with chest leads by conventional electrocardiography This enables conclusions concerning the position of the cardiac electric axis to be drawn from results recorded with these three leads, and finally because the lead system is not too difficult to attach quickly Resistors of 50 kΩ were connected in the classical manner to the central terminal. A lead selector constructed in our laboratory made the changing of leads possible.

The Electrocardiocorder Model 350 A was used for recording The original battery of Avionics was replaced by a larger NiFe-accumulator which was connected to the recorder with an earthed wire and an extra plug in jack. This provided power enough for recordings of more than 100 hours without charging. Permatone TX-S-8 magnetic tape was used for registration, the small reels suitable for the recorder being sufficient for 14-hour recordings.

the loudspeaker of the Akai tape recorder Once again an audio-visual presentation is utilised, and this facilitates the detection *of momentary alterations of the recorded* ECG For this oscilloscopic display the Atlas 46 A oscilloscope (Atlas-Werke A. G *Bremen) has* been used.

The block diagram of the electrocardi ocording and analysing procedures is pre*sented in Fig 1 The recordings of* one-millivolt rectangular calibration pulse made with Mingograph 24 and the Electrocardio*corder the latter recording written out by* means of the Electrocardiocharter and the MV 1 link, are compared in Fig. 2. We *have tested the responses of both the* scanner unit and the MV 1 link, by making an Electrocardiocorder recording with a sine *wave pulse generator The voltage losses* detected in the middle of the frequency range of the scanner ECG output being *compensated in the construction of MV 1* amplifier

In practice, the Electrocardiocharter is throublesome to use, because the original recording must be removed from the deck of the scanner to that of the charter and the interesting point of the recording can thus be lost. The detecting of such a point can be difficult without an oscilloscope control, and involves the expense of much time and ECG paper In the MV 1 system the final signal can be continuously followed with an oscilloscope and a loudspeaker and only the essential segments need to be printed on paper The original recording can stay on the scanner deck all the time. These practical difficulties have been par tially eliminated in the Composite Electrocardioscanner Model 651 of Avionics, which includes both the scanner and the charter units.







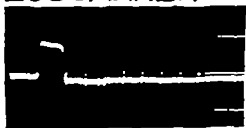


Fig. 2. Mingograf 24 Electrocardiocharter MV 1 and Electrocardioscanner reproductions of the 1 mV/1 cps calibration pulse of One-Millivolt Calibrator

ADJUSTMENTS OF THE APPARATURE FOR THE PRESENT STUDY

Recording

The AVSEP scanner analysis presumes an undisturbed tape recording of the ECG signal. Three major disturbing factors must be eliminated 1) the alternatig current noise 2) the muscle potentials and 3) *the wandering of* the base line. These factors become particularly important when we have an unco-operative subject like a new born infant, when we must continue our

ing takes place in the MV 1 link, the pulse becoming rounded in the final presentation.

Besides the standard pulse of 1 cps, another higher calibration frequency is useful when heart rates of small infants are studied. In the present investigation the scanner unit was also calibrated by means of a tape recording of a pulse with frequency of 2 cps, which gives a rate of 120/min, a typical heart rate of newborn infants.

It is unpractical to record the calibration pulse in the middle of a long ECG recording. Thus, in contrast to conventional electrocardiography the voltage response of the whole tape cannot be checked. Therefore a defective and nonquantitatively magnetized tape segment can be responsible for sudden voltage drops, towards which a reserved attitude must be taken.

Timing error

The clock of the scanner (and charter), is moved mechanically by the tape which turns a small pulley on the deck of the machine. Thus, the exactness of the clock depends upon the friction between the tape and the pulley. Also the properties of the reels, brakes, capstans, and pinch rollers, both in the recorder and analysers, cause some timing errors. These have been studied by Hinkle et al. [15] and a cumulative timing error of +14 to —8 per cent has been presented for Model A recorders. This error is not a constant one during the course of the recording. Our equipment gave an error up to + 12 per cent at the beginning, which diminished to zero to the end of the recording, when Permatone TX-S-8 tape was used. We took off the spin from the take-up reel axis thus there was friction between the axis and the reel, instead of the axis and the rubber loop of the tape transport mechanism. The traction effect of the take-up reel was diminished, and a better time stability of the tape transport was produced. The timing errors could be corrected by means of a regular marking, e.g. lead changing, and exact diary keeping.

Base line error

The base line of the scanner oscilloscope is not a straight one as can be seen in Fig. 3. There is a disturbing sine wave of low amplitude present even in the first amplification stage, and this must be kept in mind when analysing S-T and T alterations. This distorted base line may be partially responsible for the pre-T notch, an artifact found in one half of the tape recordings studied by Gilson et al. [27]. It does not disturb the analysis, if the duration of S-T segment is not the subject of measurements. The sine wave of the base line is somewhat amplified in the MV 1 presentation. We have not tried to correct this disturbing factor because it seems to be a construction peculiarity in all the equipment we have used.



Fig. 3. The deformed base line of the AVSEP display of Electrocardioscanner: the 30 cps calibration pulse of the scanner amplified with maximal vertical gain.

Analysing procedures

The recordings obtained were scrutinised with the Electrocardioscanner Model 450 The AVSEP display of the machine was calibrated by means of 1 mV/1 cps and 1 mV/2 cps calibration pulse recordings, adjusting 1 mV equal to 10 mm, and 0.5 s equal to 50 mm on the screen. The higher heart rate scale was utilised on the Arrhythmia graph, which was calibrated according to the 1 mV/1 cps recording

The ECG configuration was examined directly by measuring the time and voltage quantities on the screen and, when necessary the pattern was photographed with an Exa camera (Ihagee, Dresden) on Kodak Tri X film with a close-up time of 1/25 s. The comparison of the values obtained directly and those measured on the exposures showed that sufficient accuracy was achieved by measuring the quantities directly 0.5 mm was the minimum unit in these measurements.

Suddenly appearing electrocardiographic alterations (e.g rhythm irregularities, S–T and T alterations) were photographed on the AVSEP oscilloscope. This is not very often elucidating, because a large group of electrocardiographic complexes are superimposed on the AVSEP screen during the rapid play back. Therefore the interesting portions of the recording were written out on paper mainly by means of the MV 1 method. For calibration and comparison, the 1 mV/1 cps pulse and the beginning pattern of each recording were registered on paper by the MV 1 technique, when the scanner analysis was started. The occurrence of sudden rapid phenomena was carefully timed by the aid of the clock mechanism and the diary

The Electrocardiocharter was not used regularly in this study for printing the recorded ECG on paper To secure as much information as possible from the presentation of the recorded ECG most of the sudden irregularities were also written out using either the Electrocardiocharter 550 of the Cardiologic Laboratory of the Meilahti Clinics of the University Central Hospital of Helsinki, Finland, or the new Composite Electrocardioscanner 651 of our own clinic. The results obtained with different analysing techniques are somewhat different, and therefore data and comments are presented in the following chapters concerning the peculiarities, advantages, and limitations of the methodology used.

TECHNICAL OBSERVATIONS

Calibration

The commercial equipment is designed mainly for adults, and therefore the rate of the basal calibration pulse produced by the One-Millivolt Calibrator is 1 cps. This test pulse is of good quality in the conventional recordings as can be seen in Fig 2, where also the distortion of this pulse in the scanner charter and MV 1 reproductions is demonstrated. The originally rectangular pulse becomes deformed in the scanner so that there is a small spike of 0 1 mV in the rising loop, and a droop of similar magnitude in the descending loop These artifacts are more marked in the newer models of Electrocardioscanner Electrocardiocharter and Composite Electrocardioscanner than in the apparatus mainly employed in this study On the other hand, some damp-

ing takes place in the MV 1 link, the pulse becoming rounded in the final presentation.

Besides the standard pulse of 1 cps, another higher calibration frequency is useful when heart rates of small infants are studied. In the present investigation the scanner unit was also calibrated by means of a tape recording of a pulse with frequency of 2 cps, which gives a rate of 120/min, a typical heart rate of newborn infants.

It is unpractical to record the calibration pulse in the middle of a long ECG recording. Thus, in contrast to conventional electrocardiography the voltage response of the whole tape cannot be checked. Therefore a defective and nonquantitatively magnetized tape segment can be responsible for sudden voltage drops, towards which a reserved attitude must be taken.

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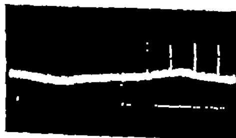


Fig. 2. The deformed base line of the AVSEP display of Electrocardioscanner: the 60 cps calibration pulse of the scanner amplified with maximal vertical gain.

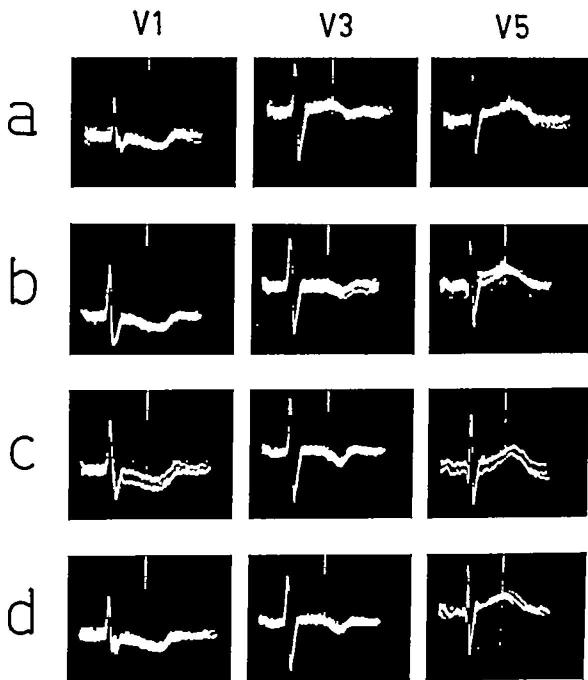


Fig. 4 Effect of posture on ECG tape recording in 6 days old premature male. Electrocardioscanner reproductions of recording performed in a) supine b) right lateral, c) prone and d) left lateral positions.

Effect of postural changes on the ECG

This effect has been noted previously e.g Holzmann [37] Changes resulting from the movement between exploring electrodes and the skin, and/or the heart, are demonstrated in the tape recordings of Fig 4 To eliminate these postural artifacts all the recordings were performed in supine position. Because of the long recording time, the infants, especially the premature ones treated in incubators, could change their posture, which must be kept in mind when analysing the tapes.

Effect of electrode impedance

A skin-to-electrode impedance of 2—20 kΩ was achieved by the careful skin preparing procedure and electrode attachment described above. The higher values were obtained at the beginning of the recording. This is of the same magnitude described for lead-Nobecutane ®— gauze electrodes by Gilson & Griffing [26]. The recommendation of the American Heart Association gives an upper limit of 6 kΩ for electrode impedance in directwriting electrocardiographs [11] but the maximal optimal impedance of Holter's device has been mentioned to be 20 kΩ [26].

COMPARISON OF CONVENTIONAL AND TAPE RECORDINGS

Examples of the ECG patterns reproduced by conventional devices and the tape recording devices of Holter were described by Gilson et al. [27]. A conventionally recorded ECG in V5 and C5R—C5 leads, was compared with that recorded in C5R—C5 lead by Holter's technique. The differences between conventional and tape recording patterns were supposed to be due to the electronic characteristics of these two kinds of recording machines. Exact data, concerning the comparability of the ECG configuration recorded by means of Holter's apparature with the pattern obtained by conventional technique in the same electrode placement, are not available.

To elucidate this problem, a series of 30 healthy full-term infants, 15 boys and 15 girls, were examined at the Obstetric Department of the District Hospital of Loimaa. None of the babies showed any signs of cardiac anomaly in a careful physical examination. The average birth weight of the material was 3450 g and the average age was 3 / days. Three chest leads, V1, V3 and V5 with a proximally placed central terminal were recorded with the subject sleeping or resting in supine position in the manner described previously in this section (page 18). With the same electrode attachment, recordings were carried out by means of a conventional Mingograph 24 electrocardiograph (Elema, Stockholm) and thereafter with Electrocardiocorder 350 A (Avionics, Los Angeles). The calibration of the conventional ECG was 1 mV equal to 10 mm, that of the tape recording was produced by the One-Millivolt-Calibrator. The paper speed in the Mingograph was 25 mm/s, the recording time lasting approximately 5 s. Each tape recording included 10 minute segments for each of the three leads.

The durations of P, P—R interval and QRS, and the amplitudes of P, Q, R, S, S—T deviation, T and U deflections were measured in the conventional recordings. The tapes were analysed in the way explained in analysing procedures (page 20). The data mentioned above were directly measured on the ECG oscilloscope of the scanner during the play-back. The analysis was performed by means of both Electrocardioscanner Model 450 and Composite Electrocardioscanner Model 651. The former was coupled to the MV 1 link, the latter includes the charter unit. The determinations of the electrocardiographic quantities were also made in the MV 1 and charter reproductions.

The data were punched on cards and the information was processed in an IBM 1130 computer. The data of the

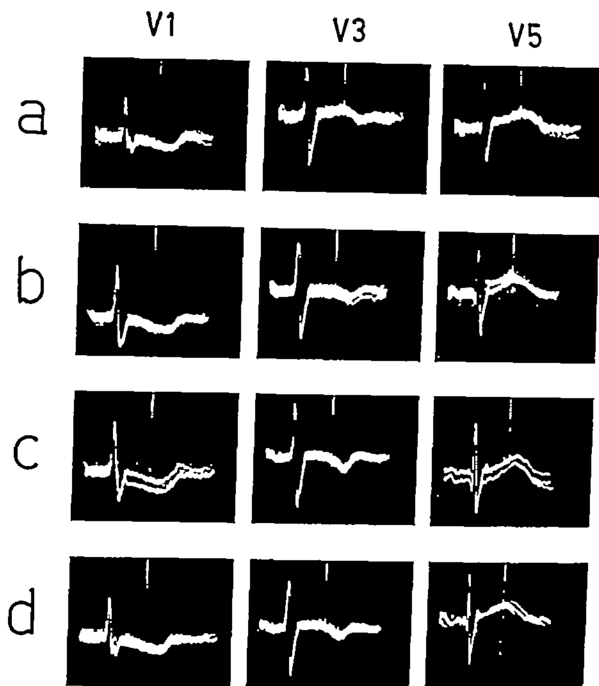


Fig. 4. Effect of posture on ECG tape recording in 6 days old premature male. Electrocardioscanner reproductions of recording performed in a) supine b) right lateral, c) prone and d) left lateral positions.

Effect of postural changes on the ECG

This effect has been noted previously e.g Holzmann [37] Changes resulting from the movement between exploring electrodes and the skin, and/or the heart, are demonstrated in the tape recordings of Fig 4 To eliminate these postural artifacts all the recordings were performed in *supine position.* Because of the long recording time the infants, especially the premature ones treated in incubators, could change their posture, which must be kept in mind when analysing the tapes.

T wave (main or initial deflection)

ECScanner 450	—0.11	0.18	0.20 — —0.45	—0.08	0.17	0.25 — —0.30	0.12	0.11	0.20 — —0.20
Mingograf 24	—0.13	0.21	0.40 — —0.55	—0.11	0.18	0.25 — —0.50	0.14	0.14	0.50 — —0.30
ECScanner } 651	—0.12	0.17	0.30 — —0.45	—0.08	0.14	0.25 — —0.30	0.12	0.12	0.30 — —0.25
ECCharter } 651	—0.12	0.17	0.20 — —0.50	—0.08	0.15	0.20 — —0.40	0.11	0.13	0.30 — —0.35
MV 1	—0.13	0.21	0.23 — —0.50	—0.12	0.19	0.25 — —0.50	0.12	0.15	0.45 — —0.35

Deviation of S-T segment

ECScanner 450	—0.02	0.03	0.00 — —0.10	—0.003	0.01	0.00 — —0.05	0.04	0.05	0.15 — 0.00
Mingograf 24	—0.05	0.08	0.00 — —0.25	—0.02	0.08	0.10 — —0.20	0.03	0.05	0.20 — —0.05
ECScanner } 651	—0.03	0.03	0.00 — —0.10	—0.01	0.03	0.00 — —0.10*	0.04	0.05	0.20 — 0.00
ECCharter } 651	—0.03	0.05	0.00 — —0.20	—0.005	0.02	0.00 — —0.05	0.04	0.05	0.20 — 0.00
MV 1	—0.03	0.05	0.00 — —0.21	—0.01	0.04	0.00 — —0.15	0.04	0.08	0.20 — 0.00

Difference almost significant, ** significant, *** highly significant.

Electrocardioscanner 450 reproductions were compared with the corresponding values of 1) the conventional Mingograph 24 recordings 2) the scanner presentations of Composite Electrocardioscanner 651 3) the charter presentations of the same and 4) the write out series of MV 1 system. The significance of differences between the series was tested with the t test. If the risk (p) was

- $p < 0.05$ the difference was called almost significant,
- $p < 0.01$ the difference was called significant and
- $p < 0.001$ the difference was called highly significant.

Results

In the comparison of the five different ECG reproductions, the corresponding durations of P wave, P—R interval, and QRS interval were found to be equal.

The mean voltages, standard deviations, and ranges of P R, S, and T waves and S—T deviations in the three chest leads, reproduced by the different tecniques, are presented in Table I, where the result of the t test is also given. No significant difference in the P wave reproduction could be demonstrated between the different techniques. The values of the negative components of 9 cases of diphasic P_{V1} are lacking in the table, but the behaviour of this negative part of the deflection proved to be the same as that of the positive one.

No Q waves were found in the V1 lead, and only in two cases was a miniature Q present in the V3 lead. The only information concerning the Q wave could be obtained from the 18 patients with Q_{V5}. The mean Q_{V5} in the conventional recording was 0.10

Table I. Amplitudes of P R, S and T waves, and S T deviations (mV) in 30 conventional and tape recording reproductions of V1, V3, and V5.

P wave (positive deflection)

Reproduction	V1			V3			V5		
	mean	S.D	range	mean	S.D	range	mean	S.D	range
ECScanner 450	0.07	0.04	0.20 — 0.02	0.09	0.05	0.20 — 0.03	0.07	0.04	0.20 — 0.02
Mingograf 24	0.08	0.06	0.30 — 0.02	0.11	0.06	0.25 — 0.03	0.08	0.06	0.30 — 0.03
ECScanner } 651	0.07	0.04	0.20 — 0.01	0.09	0.05	0.20 — 0.03	0.07	0.05	0.25 — 0.02
ECCharter } 651	0.07	0.04	0.20 — 0.02	0.08	0.04	0.20 — 0.03	0.06	0.04	0.15 — 0.02
MV 1	0.08	0.05	0.22 — 0.02	0.10	0.06	0.25 — 0.05	0.06	0.04	0.20 — 0.03

R wave

Reproduction	V1 mean	V1 S.D	V1 range	V3 mean	V3 S.D	V3 range	V5 mean	V5 S.D	V5 range
ECScanner 450	1.12	0.41	1.90 — 0.60	1.39	0.35	2.00 — 0.50	0.89	0.37	1.60 — 0.30
Mingograf 24	1.20	0.45	2.15 — 0.65	1.70	0.51	2.80 — 0.70*	1.04	0.47	2.00 — 0.35
ECScanner } 651	1.09	0.41	1.80 — 0.50	1.34	0.34	1.90 — 0.45	0.87	0.38	1.60 — 0.30
ECCharter } 651	1.04	0.42	1.90 — 0.50	1.28	0.36	2.00 — 0.40	0.83	0.38	1.65 — 0.25
MV 1	0.97	0.36	2.00 — 0.44	1.18	0.29	1.80 — 0.44	0.75	0.32	1.33 — 0.25

S wave

Reproduction	V1 mean	V1 S.D	V1 range	V3 mean	V3 S.D	V3 range	V5 mean	V5 S.D	V5 range
ECScanner 450	0.57	0.25	1.00 — 0.10	0.94	0.20	1.50 — 0.60	0.77	0.20	1.20 — 0.30
Mingograf 24	0.78	0.54	2.60 — 0.10*	1.58	0.52	2.90 — 0.65 **	1.19	0.49	2.40 — 0.20*
ECScanner } 651	0.61	0.26	1.10 — 0.10	0.98	0.19	1.40 — 0.60	0.81	0.19	1.20 — 0.40
ECCharter } 651	0.49	0.23	0.90 — 0.05	0.88	0.27	1.60 — 0.50	0.64	0.20	1.00 — 0.25
MV 1	0.49	0.25	1.00 — 0.05	0.83	0.24	1.25 — 0.45	0.65	0.25	1.16 — 0.17*

T wave (main or initial deflection)									
ECScanner 450	−0.11	0.18	0.20 — −0.45	−0.08	0.17	0.25 — −0.30	0.12	0.11	0.30 — −0.20
Mingograf 24	−0.13	0.21	0.40 — −0.65	−0.11	0.19	0.25 — −0.50	0.14	0.14	0.50 — −0.20
ECScanner 651	−0.12	0.17	0.20 — −0.45	−0.08	0.14	0.25 — −0.30	0.12	0.12	0.30 — −0.25
ECCharter 651	−0.12	0.17	0.20 — −0.50	−0.08	0.15	0.20 — −0.40	0.11	0.13	0.30 — −0.25
MV 1	−0.13	0.21	0.33 — −0.60	−0.12	0.19	0.25 — −0.50	0.12	0.15	0.45 — −0.25
Deviation of S–T segment									
ECScanner 450	−0.02	0.03	0.00 — −0.10	−0.002	0.01	0.00 — −0.05	0.04	0.05	0.15 — 0.00
Mingograf 24	−0.05	0.08	0.00 — −0.25*	−0.02	0.08	0.10 — −0.30	0.02	0.05	0.20 — −0.05
ECScanner 651	−0.03	0.03	0.00 — −0.10	−0.01	0.03	0.00 — −0.10*	0.01	0.05	0.20 — 0.00
ECCharter 651	−0.03	0.05	0.00 — −0.20	−0.005	0.02	0.00 — −0.05	0.04	0.05	0.20 — 0.00
MV 1	−0.03	0.06	0.00 — −0.21	−0.01	0.04	0.00 — −0.15	0.04	0.06	0.20 — 0.00

Difference almost significant, ** significant, *** highly significant.

Electrocardioscanner 450 reproductions were compared with the corresponding values of 1) the conventional Mingograph 24 recordings 2) the scanner presentations of Composite Electrocardioscanner 651 3) the charter presentations of the same and 4) the write out series of MV 1 system. The significance of differences between the series was tested with the t test. If the risk (p) was

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Results

In the comparison of the five different ECG reproductions, the corresponding durations of P wave, P—R interval, and QRS interval were found to be equal.

The mean voltages, standard deviations, and ranges of P R, S and T waves and S—T deviations in the three chest leads, reproduced by the different tecniques, are presented in Table I, where the result of the t test is also given. No significant difference in the P wave reproduction could be demonstrated between the different techniques. The values of the negative components of 9 cases of diphasic P_{V1} are lacking in the table, but the behaviour of this negative part of the deflection proved to be the same as that of the positive one.

No Q waves were found in the V1 lead, and only in two cases was a miniature Q present in the V3 lead. The only information concerning the Q wave could be obtained from the 18 patients with Q_{V6}. The mean Q_{V6} in the conventional recording was 0.10

(range 0 05—0.50) mV and the corresponding value in the Electrocardioscanner 450 presentation was 0 16 (range 0 00—0.35) mV Although too small for inferences, the group of Q values revealed no significant difference between the five ECG presentation techniques.

The voltages of the main ventricular depolarization deflections, R and S waves are generally lower in the tape recordings than in the conventional recordings. The ability to repeat these deflections seems to be equal in both Electrocardioscanner Model 450 and the scanner of Composite Electrocardioscanner 651 Considerable voltage deficits are produced by both printing methods, the charter of Composite Electrocardioscanner 651 and the MV 1 chain. In the case of the R wave the difference becomes significant between the scanner display and the conventional recording as the deflection reaches the value 1 70 mV in the conventional ECG (the mean voltage of R_{V3} in the table) A significantly unequal reproductability is also found in the comparison of the repeating characteristics of the scanner and those of the MV 1 equipment at the level 1.39 mV in the scanner presentation (the mean voltage of R_{V3} in the table) The voltage losses of the R wave in the tape recording become more marked as the magnitude of the R wave increases and the most prominent voltage deficit is produced by means of the MV 1 method.

The ability to reproduce the S deflection seems to be even lower than that of the R wave in the tape recording instruments, when compared with the conventional ECG recording technique Almost significant voltage deficit is detected in the scanner display of S_{V1} and highly significant ones in those of S_{V3} and S_{V5}. Still more distortion is produced by the writers, although almost significantly by the charter in S_{V1} reproduction, and by the MV 1 system in S_{V3} and S_{V5} reproductions.

The relations of the Electrocardioscanner 450 and the Mingograph 24 presentations of the R and S waves in V1 V3 and V5 leads are given in Fig 5

According to the values shown in Table I the ability to reproduce the T wave configuration is statistically equal in all the techniques mentioned above The table includes only the initial deflections of the diphasic T waves, which appeared 5 times in V1 6 times in V3 and 7 times in V5 The results concerning the calculations performed in the terminal portions of these diphasic T waves are similar to those presented in Table I. The polarity of the T wave is always the same in corresponding ECG reproductions The shape of the T deflection is hard to compare without an analog to-digital converter but in a rough inspection, the write out of the MV 1 chain closely resembles the conventional ECG recording in this series.

At the end of the QRS complex there is often an extra upright deflection in the scanner and charter presentation of the tape recording It will be called the post-S spike in this investigation. This spike is a peculiarity of the scanner and charter reproductions, it is not found in conventional Mingograph 24 recordings and it does not appear in the recordings written out by means of MV 1 equipment. The incidence and magnitude of the post-S spike are given in Table II. In this material it is most frequent in the V3 lead, where the voltages of the R and S waves are the greatest. It is more frequent and higher in the display of the newer scanner than in that of the older model 450 Its

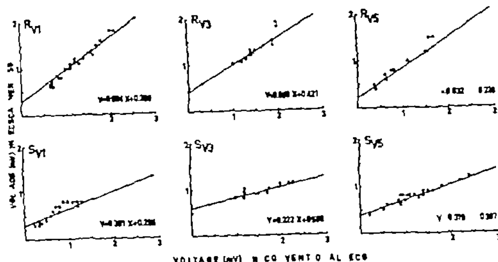


Fig. 5. Regressions of R and S wave voltages in V1, V3, and V5 leads calculated from the values of Mingograf 34 recordings and corresponding Electrocardioscanner reproductions of 30 newborn infants.

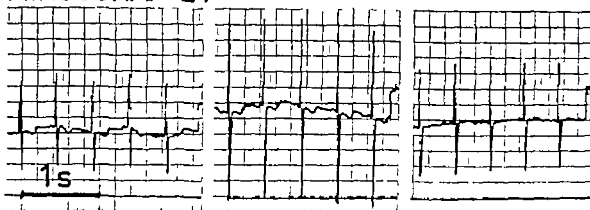
incidence and magnitude are reduced in the charter procedure.

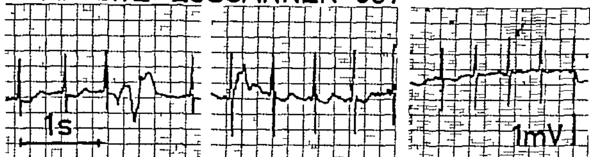
Depression of the S—T segment was present in the V1 lead in the conventional ECG of 13 infants, in the V3 lead there were 7 cases of S—T depression, and in the V5 lead the S—T deviation was positive in 6 infants and negative in one. The values of S—T deviations in different recordings are presented in Table I. Calculations have been made for the whole population. An almost significantly lower ability to reproduce S—T_{V1} deviation is established in the scanner display when compared with conventional recording. The MV 1 reproduction best resembles conventional ECG in the S—T and T regions. However the material is small and the S—T deviations are of low voltage. Thus, far reaching conclusions cannot be made according to these results. Conventional and tape recorders of this type do not repeat S—T deviations equally but at least the polarity of the deviation seems to be equal.

The U wave appeared *only* in V3 and V5 leads. There were 7 infants

Table II. The incidence and amplitude of the post-S spike in 30 ECG tape recordings of three chest leads reproduced by Electrocardioscanner 450 and Composite Electrocardioscanner 451.

	Electrocardioscanner 450			Composite Electrocardioscanner 451					
				scanner			charter		
Lead	No.	Mean (mV)	Range (mV)	No.	Mean (mV)	Range (mV)	No.	Mean (mV)	Range (mV)
V1	11	0.08	0.03—0.15	18	0.09	0.05—0.20	9	0.08	0.05—0.20
V3	18	0.11	0.03—0.20	27	0.13	0.05—0.30	24	0.10	0.05—0.20
V5	14	0.07	0.03—0.10	20	0.08	0.05—0.20	18	0.06	0.03—0.10





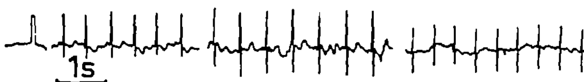


Fig. 6 Comparison of Mingograf 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450 — MV 1 technique

with U_{V3} in some of the 5 reproductions, but only 2 cases with U_{V3} in all cor responding reproductions. U_{V3} was detected in 2 infants, and it was not repeated correspondingly at all. The maximal amplitude of this deflection was 0 10 mV The comparison of Mingograph 24 recording and corresponding tape recording reproduced by Composite Electrocardioscanner 651 and Electrocardioscanner 450—MV 1 technique is presented in Fig 6

Comments

The values obtained by conventional technique which are presented in Table I, are of the same magnitude as those reported by Ziegler [11?] Wasserburger [110] and Walsh [104 107] The means and maximum values of the R and S waves seem to be a little lower in this material, as they were in the earlier study of our group [98]

A considerable attenuation of the

voltages of the R wave, and particularly the S wave, is found in reproductions of tape recordings when compared with corresponding conventional electrocar diograms. An explanation for these voltage distortions is obviously the restricted frequency response (0.5—100 cps) of the Electrocardiocorder. The recommendations of the American Heart Association [9] call for a frequency response of 0.05 — over 500 cps for direct writing electrocardiographs, and that of frequency modulated tape recorders must reach the value of more than 100 cps. According to the recorder scanner and recorder-charter system frequency response curves of Hinkle et al., the *effective* frequency range is 0.5—50 cps [35]. Thus a noticeable amount of the electrocardiographic frequency spectrum falls outside the response of this tape recording equipment.

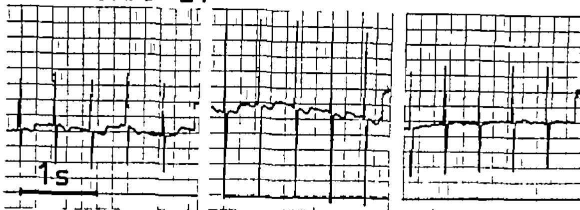
The effect of poor high-frequency response on ECG has been reported to be an increasing attenuation of R and S voltages with decreasing frequency response. The effect on the amplitude of the S deflection is more marked [53]. In ECG writers the mass of the stylus and its friction against the paper further limit the high-frequency response below the limits of the circuitry. The results of the present investigation are in agreement with these facts and also with the report of Hinkle et al. [35].

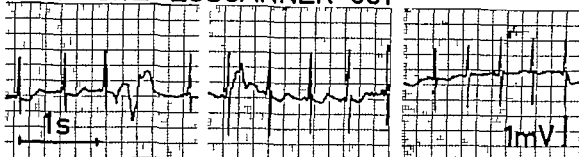
The restriction of low frequency response of the electrocardiograph leads to inaccuracy in repeating wave forms containing lower frequency components, i.e. P S—T and T (U) deflections, correctly. Thus a progressive attenuation of T wave voltage, and also an increase of S wave amplitude, have been reported to be produced by deteriorating low frequency response [53]. Only a minimal and not significant deficit of T wave amplitude was observed in the tape recording presentations of the present study. A minimal S—T segment depression and post T sag have been also considered as artifacts caused by degenerated low frequency cut-off [35 53]. These findings have already been described in Electrocardiocorder scanner presentations [27]. Significant differences were found in the present investigation between the corresponding recordings in their ability to reproduce S—T deviation, but the S—T depressions did not prove to increase in tape recording reproductions. Because of the inaccuracy of the information available concerning the reproductibility of the S—T segment in the instruments of Holter Avionics, and because of the importance of this segment in the diagnosis of coronary heart diseases, this area calls for more investigation.

Attention has not been paid earlier to the post-S spike, a common finding in the present study. This spike is a small overshoot after a prominent S wave, and deep S waves are not so common in left precordial leads among adults investigated earlier by means of this technique.

CONCLUSIONS

The Electrocardiocorder-AVSEP tape recording system of Holter Avionics is a valuable tool when long term ECG recordings are to be studied. By means of the modified electrode design, and in standardized test conditions, an interference-free recording of unipolar chest leads (V1, V3 and V5) can be obtained. Suddenly appearing altera





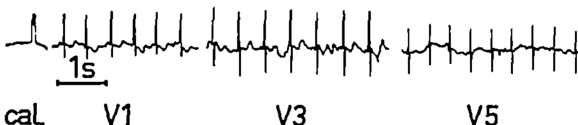


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THE HEAD INJURY POPULATION

In spite of the omission of some cases of acute head injury with clear cerebral symptoms, the author maintains that the head injury population probably represents such cases of acute head injury as are usually reported by parents in practical clinical child psychiatric work

However the extent to which such reported acute head injuries represent actual acute head injuries of a certain degree of severity is questionable. Of the part of the head injury population cared for in hospital 85 % were judged on telephone interview to have had a cerebral concussion, compared with 55 % of those cared for at home. For this and other reasons it may be assumed that whereas the head injury population contains the majority of acute head injuries associated with primary cerebral symptoms, it includes in addition a great many cases of less serious head injuries, mostly intermingled with the cases of cerebral concussion cared for at home

THE TELEPHONE INTERVIEW

A clinical interview by telephone need not necessarily be less satisfactory in any significant way from an interview in which the participants are present to each other To be sure, in evaluating the information obtained, the interviewer does not have the aid of visual non verbal communication from the respondent but this becomes less important the more concrete and less value loaded the questions are. Presumably the respondent feels more anonymous in a telephone interview than in a personal interview and is probably inclined to give an adequate and unreserved anamnesis

Faced with the necessity of interviewing the parents of 776 children in a limited period of time, there was no practical alternative to the use of telephone interviews

The response was 99.5 %. It is the author's impression that the parents not only permitted themselves to be interviewed but were usually eager to give a complete and correct account of the traumatological factors associated with the acute head injury in question.

The answers to the questions as to the child's age at the time of the acute head injury and the circumstances of the accident were somewhat uncertain, since the accident had often occurred many years before the interview took place, but the author does not believe there is any reason to question their value

This however is not the case regarding the information about primary cerebral symptoms In general the parents could not remember whether the child had vomited once or several times, if he had been dizzy or had had headache or had been merely generally affected On the other hand, the parents clearly remembered the degree of severity they attributed to the situation, and in most cases they could recall whether the child had vomited or had been unconscious.

If the child had been hospitalized for the head injury this would be expected to influence the parents recollection of the symptoms for several reasons. The

reassuring, or disturbing, effect of the child's being cared for by others, combined with the fact of hospitalization itself and all its implications for the child and the family would probably lead to a more firmly imprinted mental image of the primary cerebral symptoms than in the cases in which the child was not cared for in hospital.

For children who were reported by telephone interview to have been unconscious in connection with the acute head injury it was reported in the personal interview with the parents in the child psychiatric section of the investigation that the accident had occurred in the immediate vicinity of a parent in 74 % of the cases cared for at home but in only 42 % of those cared for in hospital This might be expected to have led to more dramatic or firmly imprinted mental images on the part of the parents of the children cared for at home compared to the parents of the children with comparable cerebral symptoms cared for in hospital.

The question of the reliability of the retrospective information obtained from the parents regarding primary cerebral symptoms is of critical importance for the value of the investigation. The same is true of the question whether the information obtained from the parents of children cared for at home is comparable to that obtained from the parents of children cared for in hospital

These questions can be answered to some extent, since information about primary cerebral symptoms was submitted on several occasions at intervals of six months to one and one-half years on the questionnaire for the primary material, by telephone interview for the head injury population and in the interview in the child psychiatric section of the investigation for the children who were reported on telephone interview to have been unconscious in connection with the acute head injury moreover for the children who had been admitted to hospital, information was available in the hospital record

In comparing the information obtained by questionnaire and by telephone with respect to the degrees of severity of the reported primary cerebral symptoms, it was impossible to make the comparison for each symptom individually The author's evaluation of the severity of the head injury in less severe cases (= unconsciousness for up to 5 minutes and no other primary cerebral symptoms of a degree of severity comparable to the unconsciousness) and in more severe cases (= unconsciousness for 5 minutes or more and/or other primary cerebral symptom(s) of comparable severity) when based on information obtained by telephone interview proved to be poorly correlated with the conclusions reached on the basis of information obtained by questionnaire.

Table 3 gives the degree of correlation between information obtained by telephone interview and that obtained from the hospital record, as well as between information obtained by telephone and that obtained in the interview with the parents (child psychiatric section of the investigation) with respect to some of the primary cerebral symptoms. (Severe head injury was defined as above.)

It is immediately clear from the table that the reliability is poor so poor that the grading of head injury according to

Table Correlation between information given by questionnaire (Q) and that given by telephone interview (T) regarding the occurrence of unconsciousness associated with head injury

HEAD INJURY POPULATION CARED FOR IN HOSPITAL

Unconsciousness (+)

		Q +	Q —	tot
T	+	74	27	101
T	—	3	78	81
	tot	77	105	182

Phi = 0 72

HEAD INJURY POPULATION CARED FOR AT HOME

Unconsciousness (+)

		Q +	Q —	tot
T	+	103	67	170
T	—	32	39	424
	tot	135	459	394

Phi = 0 67

The correlation coefficient, PHI expresses the agreement between information obtained in the respective manner

the results of the epidemiologic survey is worthless, and so poor that selecting a smaller number of more severe acute head injuries for further investigation on this basis would not have been possible. The correlation coefficient, PHI varies betwen 0 14 and 0.57

It is also apparent that the reliability is poorer throughout for the investigated population cared for at home than for the investigated population cared for in hospital

Whereas the reliability of data on the duration and intensity of primary cerebral symptoms is poor this does not seem to be true of data on the occurrence of concrete and easily defined symptoms like unconsciousness. The information about unconsciousness associated with the head injury that was obtained by telephone interview for all the children in the investigated population cared for in hospital was confirmed by the hospital record in 63 of 75 cases, or 84 %, and in the interview in the child psychiatric section of the investigation in 94 of 97 cases or 97 % The correlation between the information obtained by questionnaire and that obtained by telephone interview regarding unconsciousness is shown for the entire head injury population in Table 2. Although a response of don t know was returned on over 10 % of the questionnaires but was not accepted in the telephone interviews, the value of PHI was 0.72 for the head injury population cared for in hospital and 0 67 for the head injury population cared for at home

It is fortunate that with respect to the occurence of unconsciousness there is no marked difference in reliability between the data for the children cared for in hospital and those cared for at home and that the degree of reliability is fairly satisfactory Namely acute head injuries of a certain minimal degree of severity were selected for further investigation using unconsciousness in association with head injury as the criterion of this minimal degree of severity

The validity of the concept of acute head injury associated with primary

Table 3 Correlation between information obtained by telephone interview and that obtained from the hospital record and by interview with the parents respectively concerning the duration and intensity of the primary cerebral symptoms associated with head injury in the investigated population cared for in hospital (IH) and in the investigated population cared for at home (IO)

		Hospital record	Interview with parents	
		IH	IH	IO
Tele-	Unconscious at least 3 minutes	0.30	0.37	0.26
phone	Confused at least ½ hour	0.14	0.33	0.27
inter-	Repeated vomiting	0.33	0.32	0.33
view	Severe head injury (author evaluation)	0.30	0.33	0.24

The correlation coefficient, PHI, expresses the agreement between information given by telephone interview in the epidemiologic part of the investigation and information supplied for the hospital record or given during the interview with the parents in the child psychiatric part of the investigation. PHI has been calculated for IH as well as for IO

cerebral symptoms (Commotio cerebri, in severe cases, Contusio cerebri) in relation to the possibility of brain damage giving rise to psychic sequelae is one of the questions the investigation as a whole is intended to elucidate, and a discussion at this point would be premature.

On the other hand, one may pose the question whether the diagnosis of cerebral concussion can be made solely on the basis of anamnestic information about an acute head injury and the primary cerebral symptoms associated with it.

On going through the available follow up studies of less severe head injury materials, one gets the impression that information about primary cerebral symptoms has often been entirely anamnestic, and that no observations of note had been recorded at the time of the child's admission to the hospital. On going through the hospital records of the children in the investigated population cared for in hospital (See Fig. 2) the author found that the diagnosis of cerebral concussion had usually been made on the basis of information that a head injury had been associated with unconsciousness, vomiting, confusion and other primary cerebral symptoms. In the 63 cases in which unconsciousness was recorded, this was based on purely anamnestic data in 54 cases, or 86 %. The corresponding figure for vomiting was 21 of 32 cases, or 66 %, and for confusion, 17 of 30 cases, or 57 %.

Since in clinical practice the diagnosis of cerebral concussion is often made on the basis of purely anamnestic data, the author considers this to be defensible in an investigation like the present one.

THE CEREBRAL CONCUSSION POPULATION

The author intended the cerebral concussion population to represent the types of cases of acute head injury which are reported by parents in child psychiatric clinical practice, and are also

reported to have been associated with primary cerebral symptoms of a certain degree of severity (See page 31—32.)

The cerebral concussion population, however probably includes most of the children in the primary school population who had actually had such a head injury but mingled with these are children who had had less severe head injuries At least in the cerebral concussion population cared for at home, the latter were present to more than a negligible extent. Therefore the results in regard to cerebral concussion in the epidemiologic section of the investigation should be regarded as tentative

THE INVESTIGATED POPULATIONS

The material represented in the investigated populations is better defined than that in the cerebral concussion population since the telephone interview method is more reliable for establishing the presence or absence of unconsciousness than it is for evaluating the general degree of severity of primary cerebral symptoms In addition the same traumatological data were obtained on two different occasions and these can be compared in the individual case.

The populations would therefore seem to represent the types of acute head injuries associated with unconsciousness that are reported in clinical practice. The author however is not certain that they represent actual acute head injuries of this degree of severity and again it must be emphasized that the results of the epidemiologic section of the investigation are to be regarded as tentative

TRAUMATOLOGICAL PART OF THE INTERVIEW WITH THE PARENTS CHILD PSYCHIATRIC SECTION OF THE INVESTIGATION

As in the telephone interview there was little uncertainty associated with such data as the child s age at the time of the head injury and the circumstances of the accident. The reliability of reports of individual primary cerebral symptoms, at least of reports of unconsciousness, would seem to be acceptable, as was the reliability of similar information obtained by telephone interview As in the telephone interviews, information about the duration and intensity of primary cerebral symptoms was not very reliable. For a discussion of the above and of reliability in general, the reader is referred to the part of this chapter dealing with the telephone interview

Summary

The methods and the materials in the epidemiologic section of the investigation are discussed and can be analysed to some extent since traumatological data for a given child were often obtained on several different occasions (from the hospital record by questionnaire by telephone interview and in the personal interview in the child psychiatric section of the investigation) and since the order of magnitude of omissions could be elucidated by reviewing the records of the Department of Surgery of Umeå Hospital and by the frequency of later reported acute head injury among the controls in the child psychiatric section of the investigation

The author concludes that.

The primary material represents non-oligophrenic children, 7—16 years of age, raised in a densely populated area.

The main question on the questionnaire was answered so satisfactorily that most of the children who had suffered acute head injuries associated with primary cerebral symptoms came to be included in further investigations.

The head injury population, the cerebral concussion population and the investigated populations represent acute head injuries of the types that in practical clinical work are reported on questioning to have occurred and to have been associated with primary cerebral symptoms of certain degrees of severity

The procedure of obtaining retrospective data by telephone interview long after the time of occurrence of the head injury in question is defensible and the information obtained is fairly reliable with respect to age at the time of head injury the circumstances of the accident and whether the head injury was associated with unconsciousness.

On the other hand, the method of telephone interview does not permit reliable grading of the degree of severity of the head injury not even in the investigated populations, for which information about primary cerebral symptoms was also obtained by later personal interview in the child psychiatric section of the investigation.

The cerebral concussion population and, to a lesser extent, also the investigated populations are therefore not sufficiently representative of actual acute head injuries of given degrees of severity to permit the results of the epidemiologic section of the investigation to be more than tentative.

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Table 4 Frequency in different sex and age groups in the primary school population of reports of acute head injury on the mailed questionnaire (H) of acute head injury associated with such primary cerebral symptoms (according to telephone interview) as to be evaluated by the author as cerebral concussion (C) and of acute head injury with unconsciousness (according to telephone interview) and therefore selected for the child psychiatric part of the investigation (I)

BORN	Boys				Girls			
	N	H	C	I	N	H	C	I
48—53 X	888	183	130	80	841	109	67	38
%		21 %	15 %	9 %		13 %	8 %	5 %
54—56 X	798	158	89	43	836	101	49	33
%		17 %	11 %	5 %		12 %	6 %	4 %
57—60 X	921	125	1	35	827	120	70	42
%		14 %	8 %	4 %		15 %	8 %	5 %
48—60 X	2601	446	290	158	2504	330	186	113
		17 %	11 %	6 %		13 %	7 %	5 %

N = the number of primary school children in an age-sex group
X = the number of head injuries of each type reported in such an age-sex group

and unconsciousness of five minutes to one-half hour's duration in only 10 cases. The retrospective data on primary cerebral symptoms were thus probably considerably exaggerated

The author believes, but cannot be sure, that the children whose acute head injuries were reported to have been associated with unconsciousness and who on the basis of this criterion were selected for further investigation in the child psychiatric section of the investigation represent, in a fairly satisfactory way the acute head injuries associated with unconsciousness that had actually occurred in the primary school population. The reason is that reports of the occurrence of unconsciousness are acceptably reliable, clearly more reliable than information as to the duration of unconsciousness.

The frequency in the primary school population of reported acute head injury associated with unconsciousness was 5 %. the frequencies for different ages and sexes are shown in Table 4 and the pattern is analogous to that for acute head injury with cerebral concussion.

However the age and sex distributions in the head injury population, the cerebral concussion population and the investigated populations give a poor picture of the risk for a child of a given sex and age of incurring an acute head injury of the respective degrees of severity On the basis of information as to the ages at which the children had suffered the head injuries in question (telephone interview data) and the age and sex distribution in the primary school population, the author has therefore attempted to calculate the yearly risk of acute head injuries of the respec

Results

It was reported by questionnaire that 15 % of the primary school population had previously suffered such a severe blow to the head that the parents had been seriously worried This frequency was judged to be a correct expression of how *often parents of primary school* children report an acute head injury when questioned The frequencies of reported acute head injuries for different ages and sexes are given in Table 4

For boys, the frequency increases with age for girls, it appears to be the same at different ages. In the youngest age group the frequency is the same for both sexes On the average, there are three boys to every two girls

In the telephone interview with the parents who had reported acute head injury the primary cerebral symptoms were described and it was judged wheth er cerebral concussion had been present The frequency of cerebral concussion obtained in this way was 9 % for the primary school population. This fre*quency is believed to be a correct expres* sion of how often the parents of pri mary school children report that their child has had an acute head injury associated with such primary cerebral symptoms that the diagnosis of cerebral concussion may be made retrospectively The frequencies of reported cases of cerebral concussion for different ages and sexes are given in Table 4 and follow a pattern analogous to that for acute head injuries. It cannot be stated with certainty to what extent these reported cases of cerebral concussion represent the cases of cerebral concus *sion that had actually occurred among* the children in the primary school popu lation However there is reason to be lieve that few children who had actually had a cerebral concussion came to be omitted from the cerebral concussion population On the other hand children who had in fact suffered only slight head injuries without appreciable cere bral symptoms but who came to be in cluded in the cerebral concussion popu lation can be assumed to make up a considerable part of this population, according to the discussion in the previous chapter Further evidence for this is the fact that in the investigated popu lation cared for in hospital unconscious ness of at least a half hour s duration was reported in 20 cases, and uncon*sciousness of from* five minutes to one-half hour in even more cases, on the questionnaire and by telephone inter view as well as in the personal inter view in the child psychiatric section of the investigation In the corresponding hospital records, on the other hand un consciousness of at least one half hour s duration was recorded in only five cases,

Table 6. The nature of the accident in the head injury population (H) in the cerebral concussion population (C) and in the investigated populations (I) according to information given by telephone interview

	N	CAUSE OF HEAD INJURY CHILD FELL FROM at least 2 m	½—2 m	0—½ m	vehicle	TRAFFIC ACCIDENT	OTHER
H	776 744	28 = 4 %	264 = 35 %	135 = 18 %	168 = 23 %	83 = 11 %	66 = 9 %
C	476 476	26 = 5 %	176 = 37 %	67 = 14 %	122 = 26 %	50 = 11 %	35 = 7 %
I	271 271	23 = 8 %	86 = 32 %	45 = 16 %	65 = 24 %	34 = 13 %	20 = 7 %

N = the number of children in population
= the number of children in the population for whom information was actually obtained.

Table 7. Comparison of the head injury population (H) the cerebral concussion population (C) and the investigated populations (I) with respect to the duration of unconsciousness associated with the head injury as reported by telephone interview (T) and by mailed questionnaire (Q)

		N	REPORTED UNCONSCIOUSNESS FOR at least ½ hr	5 min—½ hr	less than 5 min	NO REPORTED UNCONSCIOUSNESS
H	T	776 771	21 = 3 %	36 = 5 %	214 = 28 %	501 = 65 %
	Q	776 776	19 = 2 %	20 = 3 %	179 = 23 %	558 = 72 %
C	T	476 476	21 = 4 %	36 = 8 %	214 = 45 %	205 = 43 %
	Q	476 476	19 = 4 %	20 = 4 %	179 = 38 %	258 = 54 %
I	T	271 271	21 = 8 %	36 = 13 %	214 = 79 %	—
	Q	271 271	19 = 7 %	20 = 7 %	179 = 66 %	53 = 20 %

For explanation of the symbols, see table 6

sion is that head injuries of the least degree of severity were caused by the same types of accidents as head injuries associated with at least moderately severe primary cerebral symptoms.

When one compares the parts of the head injury population, the cerebral concussion population and the investigated populations, cared for at home and in hospital respectively one finds major differences. These differences are analogous in the different populations.

Since the investigated populations are judged to best represent head injuries of a defined degree of severity that actually occurred, they will be used as a basis for the following discussion.

It is clear from Table 9 that traffic accidents are much more likely than other accidents to cause a head injury that leads to hospital care. This is true to a lesser extent of falls from greater heights. Otherwise there is no important difference in the accident pattern for the acute head injuries cared for in hospital and those cared for at home.

The child's age at the time of head injury also plays an important role in

Table 5 Calculated risk for children of different ages and sexes of during the course of a year suffering acute head injury (H) cerebral *concussion* (C) and acute head injury with unconsciousness (I)

		The child's age				
		0 year	1—3 years	4—6 years	7—9 years	10—16 (18) years
Boys	H	0.9 %	1.7 %	1.7 %	1.6 %	1.6 %
	C	0.6 %	0.9 %	1.0 %	1.1 %	1.0 %
	I	0.2 %	0.5 %	0.5 %	0.7 %	0.7 %
Girls	H	0.9 %	1.4 %	1.2 %	0.8 %	0.8 %
	C	0.5 %	0.8 %	0.7 %	0.6 %	0.6 %
	I	0.2 %	0.5 %	0.4 %	0.4 %	0.4 %

The number of head injuries of each type reported to have occurred in children at a certain age was divided by the number of children reported by questionnaire to have passed this age. This expression of risk multipl ed by 100 gives the risk as a percentage The average risk for each age group is given i the table

tive degrees of severity These yearly incidences are given in Table 5 It is clear that the yearly incidences of more severe and of less severe acute head injuries change with the child's age in completely analogous ways The yearly incidence increases for both sexes from the low level for the infant to the considerably higher level for the toddler where for boys, it remains during the preschool years and increases further during the school years whereas the yearly incidence for girls decreases somewhat during the preschool years and then remains at the same level during the preschool and school years. In the school years the yearly risk of cerebral concussion is of the order of magnitude of 1 % for boys 1/2 % for girls

The great difference between the number of boys and the number of girls in the hospitalized head injury materials that appear regularly in the literature could, according to the results of this investigation be explained by the fact that boys of preschool and school age (but not younger boys) clearly suffer acute head injuries of all degrees of severity more often than girls.

The average degree of severity of head injury is higher in the investigated populations than in the cerebral concussion population and higher in the cerebral concussion population than in the head injury population This is clearly shown in Table 7 even taking into account the considerable uncertainty of the information about the duration of unconsciousness

On the other hand the accident patterns in these three populations are very similar from one population to another Falls of various kinds, mostly from heights or from a vehicle of some sort (bicycles, skates skis etc.) greatly predominate over traffic accidents and other types of accidents. (Table 6)

Falls from greater heights and traffic accidents are somewhat more common in the investigated populations than in the other materials, but the difference is very slight, and the general impres

Table 6 The nature of the accident in the head injury population (H) in the cerebral concussion population (C) and in the investigated populations (I) according to information given by telephone interview

	N		CAUSE OF HEAD INJURY					
			CHILD FELL FROM				TRAFFIC ACCIDENT	OTHER
	N		at least 2 m	½—2 m	0—½ m	vehicle		
H	776	744	28 = 4 %	264 = 35 %	135 = 18 %	168 = 23 %	83 = 11 %	66 = 9 %
C	476	476	26 = 5 %	176 = 37 %	67 = 14 %	122 = 26 %	50 = 11 %	35 = 7 %
I	271	271	23 = 8 %	86 = 32 %	43 = 16 %	65 = 24 %	34 = 13 %	20 = 7 %

N = the number of children in population
= the number of children in the population for whom information was actually obtained.

Table 7 Comparison of the head injury population (H) the cerebral concussion population (C) and the investigated populations (I) with respect to the duration of unconsciousness associated with the head injury as reported by telephone interview (T) and by mailed questionnaire (Q)

		N		REPORTED UNCONSCIOUSNESS FOR at least ½ hr	5 min—½ hr	less than 5 min	NO REPORTED UNCONSCIOUSNESS
H	T	776	772	21 = 3 %	36 = 5 %	214 = 28 %	501 = 65 %
	Q	776	776	19 = 2 %	20 = 3 %	179 = 23 %	558 = 72 %
C	T	476	476	21 = 4 %	36 = 8 %	214 = 45 %	205 = 43 %
	Q	476	476	19 = 4 %	20 = 4 %	179 = 38 %	258 = 54 %
I	T	271	271	21 = 8 %	36 = 13 %	214 = 79 %	—
	Q	271	271	19 = 7 %	20 = 7 %	179 = 66 %	53 = 20 %

For explanation of the symbols, see table 6

sion is that head injuries of the least degree of severity were caused by the same types of accidents as head injuries associated with at least moderately severe primary cerebral symptoms.

When one compares the *parts of the* head injury population, the cerebral concussion population and the investigated populations, cared for at home and in hospital respectively one finds major differences. These differences are analogous in the different populations.

Since the investigated populations are judged to best represent head injuries of a defined degree of severity that actually occurred, they will be used as a basis for the following discussion.

It is clear from Table 9 that traffic accidents are much more likely than other accidents to cause a head injury that leads to hospital care. This is true to a lesser extent of falls from greater heights. Otherwise there is no important difference in the accident pattern for the acute head injuries cared for in hospital and those cared for at home.

The child's age at the time of head injury also plays an important role in

T bl 8 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the age of the child at the time of head injury The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N	n	0 year	1—3 years	4—6 years	7—9 years	at least 10 years
				CHILDS AGE AT THE TIME OF HEAD INJURY				
IH	T	101	101	3 = 3 %	12 = 12 %	34 = 34 %	28 = 28 %	24 = 4 %
	i	101	97	3 = 3 %	14 = 14 %	30 = 31 %	24 = 25 %	26 = 27 %
IO	T	170	170	8 = 5 %	59 = 35 %	37 = 22 %	38 = 22 %	28 = 16 %
	i	170	156	8 = 5 %	56 = 36 %	27 = 17 %	35 = 22 %	30 = 19 %

For explanation of the symbols, see table 6

Tabl 9 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the nature of the accident. The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N	n	at least 2 m	½—2 m	0—½ m	vehicle	TRAFFIC ACCIDENT	OTHER
				CAUSE OF HEAD INJURY					
				CHILD FELL FROM					
IH	T	101	101	15 = 15 %	22 = 22 %	11 = 11 %	21 = 21 %	28 = 28 %	4 = 4 %
	i	101	93	17 = 18 %	13 = 14 %	6 = 6 %	22 = 24 %	29 = 31 %	6 = 6 %
IO	T	170	170	8 = 5 %	57 = 34 %	39 = 23 %	44 = 26 %	6 = 4 %	16 = 9 %
	i	170	154	9 = 6 %	49 = 32 %	32 = 21 %	45 = 29 %	5 = 3 %	14 = 9 %

For explanation of the symbols, see table 6

Tabl 10 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the duration of unconsciousness associated with the head injury The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N		at least ½ hr	5 min—½ hr	less than 5 mi
		DURATION OF UNCONSCIOUSNESS ASSOCIATED WITH HEAD INJURY				
IH	T	101	101	20 = 20 %	22 = 22 %	59 = 58 %
	i	101	97	19 = 20 %	26 = 27 %	52 = 54 %
IO	T	170	170	1 = 1 %	14 = 8 %	155 = 91 %
	i	170	156	—	18 = 12 %	138 = 88 %

For explanation of the symbols, see table 6

determining whether there will be hospital care. The head injuries of infants and toddlers are not cared for in hospital as often as are the head injuries of children of other ages. This difference is especially striking for toddlers For children of prepubertal and pubertal age the opposite is true, but to a lesser extent. (See Table 8)

The head injuries cared for in hospital differ from those cared for at home most decisively in that nearly half of the cases were reported to have been associated with unconsciousness of at least five minutes duration, whereas this was reported for only one-tenth of the cases cared for at home. Although these data are uncertain, the author believes that severe head injuries are much oftener the subject of hospital care than are less severe head injuries. (See Table 10)

Summary

As the discussion of methodology in the previous chapter made clear the results of the epidemiologic section of the investigation are to be regarded as tentative They apply to a material of reported acute head injuries, but it is not certain that they are representative of the acute head injuries that actually occurred.

Acute head injuries were reported retrospectively for 15 % of a primary school population, cerebral concussion for nearly 10 % and acute head injury associated with unconsciousness for 5 %. The ratio of boys to girls was three to two, the difference being due to a preponderance of older boys. The risk of suffering a cerebral concussion during the course of a year increases for boys up to school age, but remains at a lower level for girls from preschool age on. The risk is estimated as being of the order of magnitude of 1 % for a schoolboy and 1/2 % for a schoolgirl.

Slight head injuries seem to be caused by the same types of accidents as are moderately severe head injuries.

Regardless of the degree of severity of the head injuries in the material, the part of a head injury population cared for in hospital clearly differs from that cared for at home in that the average degree of severity of head injury is much greater in the part cared for in hospital, the average age of those cared for in hospital is higher and only exceptionally is a head injury due to a traffic accident not cared for in hospital. This must be kept in mind when interpreting the results of the child psychiatric section of the investigation.

Table 8 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the age of the child at the time of head injury The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N	n	CHILD'S AGE AT THE TIME OF HEAD INJURY 0 year	1—3 years	4—6 years	7—9 years	at least 10 years
IH	T	101	101	3 = 3 %	1 = 12 %	34 = 34 %	28 = 28 %	24 = 24 %
	i	101	97	3 = 3 %	14 = 14 %	30 = 31 %	24 = 25 %	26 = 27 %
IO	T	170	170	8 = 5 %	59 = 35 %	37 = 2 %	38 = 22 %	28 = 16 %
	i	170	156	8 = 5 %	56 = 36 %	7 = 17 %	35 = 22 %	30 = 19 %

For explanation of the symbols, see table 6.

Table 9 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the nature of the accident. The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N	n	CAUSE OF HEAD INJURY: CHILD FELL FROM at least 2 m	½—2 m	0—½ m	vehicle	TRAFFIC ACCIDENT	OTHER
IH	T	101	101	15 = 15 %	22 = 22 %	11 = 11 %	21 = 21 %	28 = 28 %	4 = 4 %
	i	101	93	17 = 18 %	13 = 14 %	6 = 6 %	22 = 24 %	29 = 31 %	6 = 6 %
IO	T	170	170	8 = 5 %	57 = 34 %	39 = 23 %	44 = 26 %	6 = 4 %	16 = 9 %
	i	170	154	9 = 6 %	49 = 32 %	32 = 21 %	45 = 29 %	5 = 3 %	14 = 9 %

For explanation of the symbols, see table 6.

Table 10 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared for at home (IO) with respect to the duration of unconsciousness associated with the head injury The information was obtained by telephone interview (T) and by interview in the child psychiatric part of the investigation (i)

		N	n	DURATION OF UNCONSCIOUSNESS ASSOCIATED WITH HEAD INJURY at least ½ hr	5 min—½ hr	less than 5 min
IH	T	101	101	20 = 20 %	22 = 22 %	59 = 58 %
	i	101	97	19 = 20 %	26 = 27 %	52 = 54 %
IO	T	170	170	1 = 1 %	14 = 8 %	155 = 91 %
		170	156	—	18 = 12 %	138 = 88 %

For explanation of the symbols, see table 6

included in the head injury population and the number of children in the control material for the child psychiatric section of the investigation who were nonetheless later reported to have had an acute head injury form the basis for the author's statement that the head injury population included the majority of children who at some time had suffered an acute head injury associated with appreciable primary cerebral symptoms.

The degree to which the cerebral concussion population is representative of such head injuries depends on whether the author succeeded in eliminating most of the less severe acute head injuries on the basis of information obtained by telephone interview. This is open to question, but would not seem to be the case, since it became clear that the information about primary cerebral symptoms obtained in a retrospective investigation is poorly reliable.

On the other hand, the investigated populations may be regarded as representing not only reported acute head injuries associated with unconsciousness but also head injuries of this type that actually occurred. The reason is that data on the incidence of such concrete symptoms as unconsciousness apparently have an acceptable degree of reliability.

However the author is unwilling to claim with certainty that even the investigated populations represent acute head injuries of a certain minimal degree of severity that actually occurred.

The results of the epidemiologic section of the investigation are summarized. They are valid for retrospectively reported acute head injuries of a certain minimal degree of severity but only tentative in regard to such head injuries that had actually occurred.

These results are in good agreement with Melchior's findings (76), with the overall picture presented by the available literature (page 14) and with general clinical impressions.

They give adequate answers to the epidemiological questions posed in the introduction.

Summary and discussion

The methods used in the epidemiologic section of the investigation are described. The main question on the questionnaire was intended to draw a positive answer when the primary school child had at some time suffered an acute head injury associated with appreciable primary symptoms.

The telephone interview was intended to pick out the children who had actually had an acute head injury from among those reported by questionnaire to have had such an injury and to obtain traumatological data on the children in the head injury population, the cerebral concussion population and the populations investigated in the child psychiatric section of the investigation.

The materials in the epidemiologic section of the investigation are described. The population of primary school children is regarded as representing non-oligophrenic children 7—16 years of age, raised in a densely populated area.

The head injury population is regarded as representing primary school children who were reported by their parents to have suffered an acute head injury of such a degree as to worry the parents, the cerebral concussion population as representing head injuries associated with reported primary symptoms of a certain degree of severity, the investigated populations as representing head injuries reported to have been associated with unconsciousness.

The methods and materials are discussed and analysed by comparing traumatological data obtained for the same child on different occasions by questionnaire, by telephone interview, by personal interview with a parent in the child psychiatric section of the investigation and in the case of children who had been admitted to hospital for the head injury in question from the hospital record. Because the information supplied regarding primary cerebral symptoms proved to be unreliable, it was concluded that it is not possible to grade the severity of acute head injuries on the basis of reported primary cerebral symptoms. Throughout, more severe symptoms were reported on the questionnaire and in the interviews than when the child had been admitted to hospital. Presumably the same would have been found to be true of symptoms reported for the head injury population cared for at home.

On the other hand the question whether unconsciousness had been present was answered with an acceptable degree of reliability.

The number of children who had been cared for in Umeå Hospital for acute head injuries but who failed to be

THE INVESTIGATED POPULATION CARED FOR IN HOSPITAL (IH)

The children who were reported by questionnaire to have suffered an acute head injury at some time in their lives and whose parents reported in the subsequent telephone interview that the head injury had been associated with unconsciousness and that the child had been hospitalized for the head injury were selected for the child psychiatric section of the investigation under the above designation.

Thus the investigated population cared for in hospital represents children in a primary school population whose parents, when questioned, report an acute head injury associated with unconsciousness that led to hospital care at some time during the child's life.

The extent to which it also represents such head injuries that actually occurred in the primary school population is open to question (see the chapter on discussion of methodology epidemiologic section of the investigation) but the author believes that the evidence points to its being fairly acceptable as representing such injuries.

The investigated population cared for in hospital consisted of 101 children aged 7—16 (See Table 1) The age and sex distributions were very similar to those in the parts of the cerebral concussion and the head injury populations cared for in hospital but also resembled the distributions in the parts of these populations cared for at home (see Fig. 2)

The degrees of severity of the head injuries reported by questionnaire, by telephone interview and later in the interview with the parents indicated that this material consisted of slight to moderately severe head injuries. (See Table 10)

Judging from the available records of the hospitalizations in question, however the head injuries in this material should be characterized as slight.

THE INVESTIGATED POPULATION CARED FOR AT HOME (IO)

Corresponding cases of head injury that were not cared for in hospital were selected for the child psychiatric section of the investigation under the above designation.

Thus the investigated population cared for at home represents children in a primary school population whose parents, when questioned, report that the child had at some time suffered an acute head injury associated with unconsciousness which was cared for at home.

material came to be very similar to those in the combined investigated populations.

To this end, the 4329 primary school children and the investigated population were divided according to sex and three age groups (born before 1954 1954—56 and after 1956) and a suitable number of children were drawn from each sex age group by the method of independent random selection.

The number of children in the control material was determined on the basis of the author's decision that in comparing the investigated population cared for in hospital with the control material with respect to a given variable, there should be significance at the 0 1 level when there was a percentage difference of 10 % or more in the range 10—20 %. Using the standard formulas for calculating Chi² statisticians calculated the least possible number of children in the control material that would satisfy this condition. The size of the investigation permitted no margin in the size of this group on the contrary it was necessary for the control material to be somewhat smaller than was desired.

The control material came to consist of 100 children aged 7—15 years at the time the questionnaire was sent out (see Table 1) The age and sex distributions were very similar to those in both the investigated populations (those cared for at home and in hospital respectively)

This means that in comparing an investigated population with the control material, comparisons can be made for the materials as a whole without correction for age and sex the author regards this as a definite advantage in an investigation in which there are many uncertainties in regard to what the materials represent and the value of the methods used (see the discussion of methods in the child psychiatric section of the investigation)

In comparing the investigated population cared for at home with that cared for in hospital, the fact that the materials have the nature of populations means that differences between them cannot be evaluated by calculations of significance

In comparing one of the investigated populations with the control material, of course, a significant difference means significance at the 0 1 level (as is the case throughout this study)

Table 11 Comparison between the investigated population cared for in hospital (IH) and the investigated population cared *for at home (IO) with* respect to the year the head injury occurred. The information was obtained by interview with the parents in the child psychiatric part of the investigation.

	N	n	1955 or before	1956—60	1961—65	1966
IH	101	97	6 = 6 %	28 = 29 %	54 = 56 %	9 = 9 %
IO	170	154	21 = 14 %	53 = 34 %	63 = 41 %	17 = 11 %

For explanation of the symbols, see table 6.

The extent to which the population also represents such injuries that actually occurred in the primary school population is open to question (see page 42) but the author believes that it cannot be accepted as representing such injuries since acute head injuries associated with unconsciousness were mingled with much slighter head injuries to a greater extent than was the case for the investigated population cared for in hospital The latter to be sure, also included some acute head injuries that did not lead to unconsciousness, but the very fact of hospital care gives reason to believe that the injuries were not negligible.

The investigated population cared for at home consisted of 170 children aged 7—16 years at the start of the investigation when the questionnaire was sent out (see Table 1) The age and sex distributions were similar to those in the part of the cerebral concussion population cared for at home and in the head injury population, but also resembled those in the investigated population cared for in hospital (see Fig 2)

The degrees of severity of the head injuries reported by questionnaire, by telephone interview and in the interview with the parents indicated that this material consisted of slight head injuries The author believes that, in analogy to the investigated population cared for in hospital the head injuries in this material should be characterized as very slight

In interpreting the results of this section of the study it is important to bear in mind that the investigated population cared for at home represents less severe head injuries than the investigated population cared for in hospital The periods of time that had elapsed between the head injuries and the study for the two investigated populations are shown in Table 11 The materials do not differ critically in this respect.

THE CONTROL MATERIAL (K)

The parents of 4329 children in the primary school population denied that the child had at some time in his/her life suffered such a severe blow to the head that they were seriously worried about it.

The control material was drawn from among these children by independent random selection according to the generally accepted procedure (24)

The selection process, however was conducted in such a way that the age and sex distributions in the control

material came to be very similar to those in the combined investigated populations.

To this end, the 4329 primary school children and the investigated population were divided according to sex and three age groups (born before 1954 1954—56 and after 1956) and a suitable number of children were drawn from each sex age group by the method of independent random selection.

The number of children in the control material was determined on the basis of the author's decision that in comparing the investigated population cared for in hospital with the control material with respect to a given variable, there should be significance at the 0 1 level when there was a percentage difference of 10 % or more in the range 10—20 %. Using the standard formulas for calculating Chi^2 statisticians calculated the least possible number of children in the control material that would satisfy this condition. The size of the investigation permitted no margin in the size of this group on the contrary it was necessary for the control material to be somewhat smaller than was desired.

The control material came to consist of 100 children aged 7—15 years at the time the questionnaire was sent out (see Table 1) The age and sex distributions were very similar to those in both the investigated populations (those cared for at home and in hospital respectively)

This means that in comparing an investigated population with the control material, comparisons can be made for the materials as a whole without correction for age and sex the author regards this as a definite advantage in an investigation in which there are many uncertainties in regard to what the materials represent and the value of the methods used (see the discussion of methods in the child psychiatric section of the investigation)

In comparing the investigated population cared for at home with that cared for in hospital, the fact that the materials have the nature of populations means that differences between them cannot be evaluated by calculations of significance.

In comparing one of the investigated populations with the control material, of course, a significant difference means significance at the 0 1 level (as is the case throughout this study)

General plan of the investigation

For several reasons it was desirable that the investigation should extend over broad areas of the children's lives and circumstances and to this end employ as many different sources of information as possible

First the degree of certainty of a result is strengthened if a similar result is obtained by using another method on the same material Secondly in a broad investigation a possible pattern of differences between the control material and the investigated populations is more easily recognized and defined Finally the investigation involved materials that were assembled with a great deal of care and effort and which to a considerable extent satisfy scientific standards for a statistical investigation like the present one It therefore seemed important to extract as much information from them as possible by conducting the investigation in breadth

The author wishes to emphasize how rough and uncertain the methods are that are used in a psychiatric study of a child Retrospective information about the child obtained from the parents, the teacher's evaluation of the child evaluation of the child's psychic condition and the psychic condition of the parents all may be strongly influenced by irrelevant circumstances affecting the investigator and the subject of the investigation or the respondent. In addition, the information obtained is very incomplete, as is information obtained from hospital records and other kinds of archives such as those of the child welfare board. It is clearly impossible to evaluate psychological phenomena or psychic conditions retrospectively with even a modest degree of certainty and the author maintains that an attempt to do so would be meaningless in a statistical investigation of small materials like the present study The same caution must be applied to the use of individual details in the available data and to attempts to analyse the individual child on the basis of a pattern of small details gleaned from the total available information about the child

Therefore it becomes even more important that data be gathered from as many sources as possible and extend over as broad areas concerning the child and his circumstances as possible. The author would assign a clearly higher priority to this than to the richness of detail in the data gathered

The following principal sources of information were drawn upon during the periods indicated

Home visits were carried out during the summer and fall of 1968 and the first months of 1969 the investigation at the hospital was carried out during

the fall of 1968 and the first quarter of 1969 Interviews with the teachers and review of the hospital records and the social data in various archives were carried out mainly during the spring and early summer of 1969 after all investigations at the hospital had been concluded.

It is well known that we tend to notice more readily the things we expect or wish to see. In using such subjective methods as clinical interviews or clinical evaluations of psychic states, differences between the control material and the investigated populations could easily come to reflect the author's expectations rather than actual differences if the author at the time of examination knew to which group the subject belonged.

For practical reasons it was necessary for the author himself to perform most of the evaluations, and he was naturally aware of the questions the investigation was intended to answer and could not avoid having certain personal opinions as to what the answers would prove to be.

On the other hand, it was possible in principle to withhold knowledge of a child's group membership from the author as well as from other personnel involved in the study The attempt to achieve such a blind study guided the practical design of the investigation throughout.

At the time of the first telephone contact it was especially emphasized that it was important that the author not be informed whether the child had had an acute head injury since this would influence his evaluation of the child in a possible later examination. The author asked permission to visit the family in their home in order to describe the nature of the investigation more fully and explain why discussion of the head injury itself or the fact of the absence of head injury should be deferred until all other investigations of the child had been completed. Most of the parents contacted by telephone understood this surprisingly well but it was unavoidable that in many cases the author was informed that the child had not had a head injury and in a number of cases that he had had a head injury The date and time for the home visit were set as far in the future as was practicable and the author made as many consecutive telephone calls as possible in order to minimize recall of any 'leaked' information at the time of the home visit. The intention was to maintain an interval of three to four weeks between the telephone contact and the home visit, but the interval was often two weeks and sometimes only one week or even a few days.

At the time of the home visit, the importance of maintaining a blind technique in the investigation was again emphasized, and this time the parents understood this without exception The author made note of every case in which he was aware or was made aware of whether the child had had an acute head injury

It was possible to maintain the blind technique in 321 of 353 home visits made, or in 91 %.

The date and time for the investigation at the hospital was set as far in the future as was practicable and the author made as many consecutive home visits

General plan of the investigation

For several reasons it was desirable that the investigation should extend over broad areas of the children's lives and circumstances and to this end employ as many different sources of information as possible

First the degree of certainty of a result is strengthened if a similar result is obtained by using another method on the same material Secondly in a broad investigation a possible pattern of differences between the control material and the investigated populations is more easily recognized and defined. Finally the investigation involved materials that were assembled with a great deal of care and effort and which, to a considerable extent satisfy scientific standards for a statistical investigation like the present one. It therefore seemed important to extract as much information from them as possible by conducting the investigation in breadth

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Therefore it becomes even more important that data be gathered from as many sources as possible and extend over as broad areas concerning the child and his circumstances as possible. The author would assign a clearly higher priority to this than to the richness of detail in the data gathered

The following principal sources of information were drawn upon during the periods indicated

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It is well-known that we tend to notice more readily the things we expect or wish to see. In using such subjective methods as clinical interviews or clinical evaluations of psychic states, differences between the control material and the investigated populations could easily come to reflect the author's expectations rather than actual differences if the author at the time of examination knew to which group the subject belonged.

For practical reasons it was necessary for the author himself to perform most of the evaluations, and he was naturally aware of the questions the investigation was intended to answer and could not avoid having certain personal opinions as to what the answers would prove to be.

On the other hand, it was possible in principle to withhold knowledge of a child's group membership from the author as well as from other personnel involved in the study The attempt to achieve such a blind study guided the practical design of the investigation throughout.

At the time of the first telephone contact it was especially emphasized that it was important that the author not be informed whether the child had had an acute head injury since this would influence his evaluation of the child in a possible later examination. The author asked permission to visit the family in their home in order to describe the nature of the investigation more fully and explain why discussion of the head injury itself or the fact of the absence of head injury should be deferred until all other investigations of the child had been completed. Most of the parents contacted by telephone understood this surprisingly well, but it was unavoidable that in many cases the author was informed that the child had not had a head injury and in a number of cases that he had had a head injury The date and time for the home visit were set as far in the future as was practicable and the author made as many consecutive telephone calls as possible in order to minimize recall of any "leaked information at the time of the home visit. The intention was to maintain an interval of three to four weeks between the telephone contact and the home visit, but the interval was often two weeks and sometimes only one week or even a few days

At the time of the home visit, the importance of maintaining a blind technique in the investigation was again emphasized and this time the parents understood this without exception. The author made note of every case in which he was aware or was made aware of whether the child had had an acute head injury

It was possible to maintain the blind technique in 321 of 353 home visits made, or in 91 %.

The date and time for the investigation at the hospital was set as far in the future as was practicable and the author made as many consecutive home visits

as possible in order to minimize recall of the child's group membership at the time of the investigation at the hospital

There was an attempt to maintain a three to four week interval between the home visit and the investigation at the hospital but the author often had to be content with a one to two week interval in spite of the fact that he then might remember to which group the child belonged

At the time of the investigation at the hospital, the subject of blind technique was not raised, but the author carefully avoided asking questions that could lead to the parents starting to talk about the child's possible head injury

The investigation began with a clinical examination of the child during which a conversation was conducted concerning his friends, school and interests An evaluation of the child's psychic condition was recorded along with his somatic and neurological status The child was then turned over to a psychologist for investigation The psychologist in question was unfortunately not unaware of the aims of the investigation but claimed to have been totally unaware of the childrens group membership

Meanwhile the author interviewed the parent (usually the mother) according to a plan in which questions that could be associated with head injury were deferred and were taken up only after an evaluation of the parent had been made and recorded At the very end of the interview questions were posed regarding the traumatological factors associated with the possible head injury

Note was made of the cases in which the author became aware of the group to which the child belonged before this last part of the interview It was possible to maintain the blind technique in 289 of 346 investigations performed at hospital or in 83 % During the clinical part of the investigation the author was, without exception unaware of the child's group membership

The interviews with the teachers were carried out by another investigator who at the beginning of the interviews was, without exception, unaware to which group the child belonged and who in addition, was not aware of the aims of the investigation or of its general plan To what extent the teachers informed the investigator that the child had had a head injury was not noted and cannot be judged after the fact.

Records of treatment or care of the parents at a psychiatric clinic or in a psychiatric institution were reviewed without knowing to which group the child belonged Records of somatic and/or psychiatric treatment of the children were reviewed as the journals were made available and were summarized on the same paper on which the summary of the record of care for the head injury was recorded, so that the author at the time of writing the summary was very often aware to which group the child belonged. It was considered pointless to try to avoid this since the records of admission for head injury and of treatment in the surgical clinic on other occasions were often in the same record. However when this material was first reviewed the contents of these records were read to the author omitting the record of admission for the head injury in question

Photocopies of the school dental records were obtained and their content was evaluated by another investigator without knowledge of the children's group membership but unfortunately with a certain amount of knowledge about the aims of the inquiry

Notes in the archives of the social welfare board in Umeå were reviewed by the author without knowing to which group the child belonged and such information in the archives of other communities was reviewed by another investigator who knew neither to which group the child belonged nor anything about the plan and purpose of the investigation.

The author evaluated the contents of these notes without knowing to which group the child belonged

The home visits and investigations at hospital necessarily extended over a period of time as long as half a year During such a period the more or less consciously held criteria for evaluation and the procedures for obtaining the desired information can be expected to undergo considerable development and change. At the same time it is not certain that the children investigated presented the same findings on a given occasion as they would have one half year later

These circumstances could easily produce large erroneous differences between the control material and the investigated populations.

To reduce this risk, a so-called staggered procedure was used. The children were divided into groups according to the material to which they belonged, sex and age (born before 1954 1954—56 after 1956) and from these 18 groups they were then taken in running order in such a way that each arbitrarily chosen part of the sequence came to contain representatives of the 18 groups in the same proportions as the sequence as a whole.

If it is possible to follow such a staggered sequence throughout, the risk of false differences of the above named type between the control material and the investigated populations is largely eliminated.

In practice it turned out that the approximately 50 home visits that should have been performed during a certain three-week period according to the staggered sequence system actually were performed during this period in more than 90 % of the cases, and the corresponding figure for investigations at hospital was more than 80 %.

Methods

THE HOME VISIT

Home visits were made in 353 of 371 possible cases, or in 95 %. All members of the family were not always present and therefore the omissions for certain variables are considerably more numerous than the above figure would suggest

The author's evaluation of the child the mother and the father cannot be compared with the usual type of evaluation of psychic status since, for the following reasons the usual frames of reference did not apply The evaluation was made in the home and not at the hospital the child or parent in question was not encouraged to talk about himself and his possible previous or current psychic problems the evaluation was based on observations of the respective family member in the presence of other members of the family and the period of observation was very short

By mentally disturbed at the time of the home visit the author means that he observed signs of anxiety aggressiveness apathy dullness irritability or depression in the parent in question, or that the child appeared to be physically tense restless anxious, aggressive, repressed, depressed, or very childish for his age

In most cases in which abnormal psychic states were judged to be present there were very marked signs of psychic disturbance that is, it was not a question of ordinary nervousness or tenseness. This is also apparent from the low frequencies of mental disturbance found in the control material (Table 13)

On home visit the author had a good opportunity to observe the child's relationship to the parents and the relationship of the parents to each other In a few cases — none of them in the control material — these emotional relationships were so poor that the persons in question were not able to talk to each other or erupted in aggressive attacks on each other The author regarded these homes as definitely disturbed environments which must have been directly traumatic for the child

Immediately after the home visit the author recorded his impressions of the parents, the child and the home on a form for this purpose Unfortunately this was done in such a routine way and on such a poorly constructed form that it was not possible to use this information as a basis for later classification according to type or degree of mental disturbance

The variables mentioned above thus reflect the author's subjective evaluation of whether the parents and/or the child were mentally disturbed and whether there was a seriously disturbed emotional climate in the home

The omissions in the data on the individual variables for the groups investigated were as follows

Father mentally disturbed on home visit: for IH, 34 of 101 or 34 % for IO 56 of 170 or 33 % for K, 30 of 100 or 30 %. Mother mentally disturbed on home visit. for IH, 7 of 101 or 7 % for IO 14 of 170 or 8 %, for K, 10 of 100 or 10 %. Child mentally disturbed on home visit: for IH, 13 of 101 or 13 % for IO 27 of 170 or 16 %; for K, 17 of 100 or 17 %. Disturbed emotional climate in the home: for IH, 3 of 101 or 3 % for IO 10 of 170 or 6 %; for K, 6 of 100 or 6 %.

THE CLINICAL INVESTIGATION

The author was able to carry out a clinical investigation of the child in 336 of 371 possible cases, or in 91 %. The omissions from the groups investigated were as follows: for IH 7 of 101 or 7 %; for IO 17 of 170 or 10 % for K, 11 of 100 or 11 %.

The author's physical examination of the child included the usual evaluation of a child's somatic status (general condition, height, weight, mouth and throat, lymph nodes, lungs, heart, blood pressure, abdomen, back and joints and secondary sexual characteristics) and a thorough evaluation of the neurological status (all cranial nerves, motor coordination, reflexes, tactile and vibration sense in fingers and toes, and an anamnesis in regard to sphincter function and sensory disturbances).

On the basis of the findings, a number of variables were selected for further analysis.

Height in relation to age: below two sigma, within two sigma = normal variation, over two sigma, according to Karlberg Iggbom (59)

Weight in relation to height: below, within, over the normal range of variation (= two sigma) according to Karlberg Iggbom (59)

Under the designation dysplastic traits were collected findings such as aortic stenosis, pulmonary stenosis, aplasia of the pectoralis major muscle, testicular aplasia, microphthalmia, congenital funnel breast, congenital friable watchglass nails, extremely flat feet etc.

By active upper respiratory infection the author means a combination of findings such as irritation of the mucous membranes, snuffles, cough and enlargement of the lymph nodes that are clear signs of an upper respiratory infection in a child.

By "hemispheric damage" the author means isolated and slight neurological findings such as unilateral positive Babinski or Trömner reflexes, a unilateral tendency to flexation-pronation on raising the arms, or a unilateral, non-incapacitating weakness in the legs, the arms or the face.

Under the designation other neurological findings were classed, first, cranial nerve deficiencies of all types, secondly convergence insufficiency at at least two decimeters. Other findings, mainly sensory disturbances that are hard to evaluate, were not included.

By "left-sidedness" the author means that the child preferred the left side for at least half of the following activities. writing, eating, spreading with a knife, throwing, threading a needle (stringing beads) batting a ball, landing when jumping from a height.

Finger dexterity and motor coordination were subjectively evaluated on a 3 point scale during the course of the neurological examination

During and after the physical examination the author carried on a simple conversation with the child and asked simple questions about his school companions and interests. (The child was also asked about the time of onset of change of voice or of menarche and about his or her preference for using the left side for various activities See the above) There was usually no difficulty in establishing contact with the child and a free and relaxed conversation usually developed

The designation mentally disturbed at the time of examination at hospital was applied to the children whom the author considered to be markedly tense, restless anxious, aggressive repressed depressed or childish for their ages, or with whom it was impossible to establish contact In most cases in which this designation was applied there were marked signs of psychic insufficiency that is, the disturbance was clearly more than ordinary nervousness or tenseness Although the evaluation was very similar to the usual evaluation of a child's psychic status, the frequency of psychically abnormal children found by this method was as low as 14 % in the control material

Unfortunately the author's observations were recorded on the same poorly constructed form as was used for the home visits, and it was therefore not possible to classify the psychic abnormalities found according to type or degree of severity In a few cases the author observed such fluctuations in the state of alertness, motor unrest and/or a tendency to perseverations that brain damage was suspected. Special note was made of this and it was included as a variable in the investigation

THE PSYCHOLOGICAL INVESTIGATION

A clinical psychologist accustomed to work with children was engaged for this part of the investigation The children were tested with a verbal and a nonverbal test that are parts of Westrin's Intelligence Test (WIT) (123) with two tests from the Stockholm Teachers College Diagnostic Reading and Writing Test (DLS) (71) and with the block pattern test from the Wechsler Intelligence Scale for Children (WISC) (121) The psychologist also recorded whether in her opinion the child was markedly uncooperative or had obvious difficulty in concentrating during the tests. The tests were administered in one session while the author conducted an interview with the parent.

WIT is a group intelligence test that consists of a series of three group tests for primary school grades 2—3 4—5 and 6—9 respectively The test is a factor test It was constructed with the aim of using well proven methods to develop an instrument for determining intelligence level with a high degree of reliability The abilities that the test measures are included in the conventional concept of general intelligence and have previously been correlated with among other things success in school

in a large number of investigations. Each group test contains verbal and nonverbal component tests.

The component tests used were considered to measure the following abilities. WIT I opposites and WIT III opposites are intended to measure verbal comprehension. WIT II choice measures, according to Jordan (123) the ability to think in terms of relationships in verbal material

WIT II figures and WIT III puzzle are intended to measure spatial ability WIT I classifications is intended to measure inductive ability

DLS is a modern group testing instrument intended to diagnose special reading and writing difficulties and builds on several decades of experience with similar tests It consists of a series of group tests intended for primary school grades 1—3 4—6 and 7—9 respectively

The component tests used were intended to measure the following abilities.

The dictation tests measure the ability to spell. The reading comprehension tests measure comprehension of material read silently (There is no reading comprehension test for grades 1—3)

The block pattern test from WISC is a very old one and is considered to measure spatial-inductive ability

The above tests were chosen partly because they are standardized to cover all the primary school ages. Because the time available for psychological testing was limited, only parts of the tests were used instead of the entire tests.

A verbal and a nonverbal test were chosen from WIT because each of them gives an indication of the overall level of a child's mental development, while the child with brain damage may well test much lower on the one than on the other (4 7)

A dictation test and a reading comprehension test were chosen because clinical experience has shown that the overwhelming majority of the cases of specific dyslexia diagnosed with the aid of the DLS can be diagnosed with the aid of these two component tests (47)

The block pattern test was chosen because clinical experience (4 7 21) has shown that the test is sensitive to brain damage. To be sure, it probably only detects rather extensive brain damage, but, as with other tests sensitive to brain damage, its usefulness is largely determined by the clinical experience of the psychologist.

The component tests from DLS were allowed to occupy most of the time available for psychological investigation because the pilot-study part of the questionnaire had suggested a tentative correlation between acute head injury and reading and writing difficulties. The 185 children for whom the parents reported serious reading and writing difficulties made up only 4 % of the primary school population, that is, less than half of the expected frequency (47) but head injury was reported for 22 % of these children compared with 15 % of the other primary school children. The author considered it to be of the utmost importance and worth any amount of effort to establish whether there was such a connection.

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The author intended to use the verbal and nonverbal component tests not only for evaluating the level of the child's development but also for the purpose of

diagnosing brain damage. It has namely been shown that a large discrepancy between performances on a verbal and on a nonverbal test is indicative of brain damage (4 7 10 91 109 116)

The raw score attained in the block pattern test from WISC was converted using the generally accepted method to a 20-point scale with an average score of 10 and a spread of 3 For all the other component tests, the raw scores attained were converted in the usual way to the stanine scale on which the average score is 5 and the spread 2. The points on these scales were then converted to a three point scale corresponding to above/within/below average ability according to the following: Stanine points 1—3/ 4—6/ 7—9 and block pattern points 1—6/ 7—13/ 14—20 Unless otherwise stated, this three-point scale was used throughout in analysing the results

The following variables were analysed

Spatial test from WIT verbal test from WIT dictation test from DLS reading comprehension test from DLS block pattern test from WISC, difference in stanine points between the spatial and the verbal test from WIT the same difference when performance on the verbal test was poorer uncooperativeness serious difficulty in concentrating

Since a small number of children did not wish to take part in the psychological investigation but were willing to participate in the other parts of the study the omissions were somewhat more numerous than for the author's clinical examination of the children Of a possible 371 children 326 or 88 %, were investigated. The omissions were for IH 10 children, or 10 % for IO 20 children, or 12 % for K, 15 children or 15 %.

THE INTERVIEW WITH THE PARENT

The interview mainly concerned social background factors, early development, physical health signs of early childhood neurosis and later behavioral disturbances and symptoms of psychic insuffiency

After an introductory conversation about the child's everyday routine and spare time interests, during which it was possible to establish good contact in nearly all cases, the investigation itself followed a definite order and each topic was introduced by a question with a fixed formulation that was not changed during the entire period of investigation If the answer to the question was positive or doubtful, the author shifted to a free anamnesis in order to obtain a basis for clinical evaluation of whether the established criteria for the variable in question were satisfied. If it was considered that the criteria were satisfied this was noted in the simplest way on the form for this purpose.

There were two reasons for using this procedure. The invariable use of the same introductory question with a fixed formulation and the use of clearly defined criteria of what would be considered to be a positive answer were intended to ensure the least possible change in the methodology and the grounds for evaluation during the long period of investigation. At the same time it was possible to preserve the best

features of free clinical anamnesis — personal contact with the parent and clinical evaluation of the information supplied by the parent

The disadvantage of the procedure was that the record of the information obtained from the parent became too mechanical to permit the author to later use other perhaps more clinically meaningful criteria. The limited time that was available made it necessary to accept this disadvantage.

In order to get an idea of the mother's tendency to seek outside aid for the child in various medical situations, the author had constructed a little questionnaire in which various common emergencies of childhood were described and the mother was asked whether she would have sought medical aid. Here the author had memorized all the questions and could record the answer to each by writing a letter of the alphabet. It was during this part of the interview that the author completed his evaluation of the mother's mental state and recorded it. Unfortunately this was done on the same type of form as was used for the home visit and there was thus no basis for retrospective classification according to types or degrees of severity of the mental disturbances found.

The evaluation of the mother's mental state at the time of this interview was very similar to the usual evaluation of the mental state of the mother in child psychiatric work. The author confronted the mother at the hospital, she talked for a considerable length of time about the child, the family and herself and the author was able to interrupt the routine questioning to actively draw out information about the mother's own situation as a child and any previous psychic problems she may have had.

Of course the author attempted to evaluate the mother without regard to her reports of the presence or absence of previous psychiatric difficulties, but it is obvious that such information influenced his judgment.

The mother was judged to be mentally disturbed at the time of this interview if she displayed signs of anxiety or aggressiveness, pronounced dysphorically colored melancholy depression or marked emotional and personal immaturity with abundant use of primitive defense mechanisms. In most cases it was not a question of ordinary tenseness and nervousness but of marked signs of mental disturbance. In the control material the frequency of mothers judged to be abnormal at the time of this interview was 10 %.

The following variables in the interviews with the parents were further analysed

Occupational status: the author's subjective evaluation of the occupational status of the family's breadwinner on a 5 point scale. This was done consecutively at one sitting on the entire material after the end of the investigation period on the basis of the occupations noted on the interview forms and what the occupation involves in terms of responsibility and number of subordinates.

Educational level. The author's classification of the educational level of the family breadwinner according to the following criteria. I = academic degree or equivalent. II = completion of gymnasium, some university education or

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Educational level The author's classification of the educational level of the family breadwinner according to the following criteria I = academic degree or equivalent. II = completion of gymnasium, some university education or

the equivalent III = secondary school education or the equivalent IV = trade school education evening classes or the equivalent. V = primary school education only

Incomplete home during some period in the child's life a single parent (unmarried, divorced widow or widower)

Incomplete home at the time of the start of the investigation in January 1967 (As above.)

The size of the sibling group the children who were continually present during the time the child in question was growing up

The density of the sibling group the maximum number of children under six years of age at one time

The child's position in the sibling group eldest, youngest a middle child the only child.

The mother worked outside the home before the child started school at least half time during a total of at least three years

Frequent changes of the person mainly responsible for the care of the child during the day before he started school At least two changes per year during a total of at least three years

The number of changes of residence during the child's life· moves between communities or within a community that meant a new group of companions and a new school for the child

Father physically ill during the child's life unable to work for longer periods (at least two months) or for frequently recurring shorter periods (at least two weeks)

Mother physically ill during the child's life· as above

Father mentally ill during the child's life unable to work or severely disturbed during longer periods (at least two months) or for frequently recurring shorter periods (at least two weeks)

Mother mentally ill during the child's life as above.

The age at which the child could walk across the floor without help

The age at which the child spoke two-word sentences

The school maturity test indicated that the child was too immature to start school (Administered at 6—7 years of age)

Primary enuresis never dependably dry as long as a half year and wet himself at night (or during the day) at least once a week during at least a half year after starting school

Left sidedness the child had previously had or still had, a preference for the left hand when eating, drawing, throwing, writing. At least two of these activities.

Physical illness prolonged illness or disability which, according to the author's clinical evaluation was a major handicap for the child.

Seizure states grand mal (petit mal) *febrile convulsions, affect* convulsions (44) fainting, atypical seizures with clear cerebral symptoms Seizures on at least three occasions

Refusal to eat starting in the toddler age, obvious conflict between the child and the parents at the table at least twice a week, during a half year's time.

Fear of the potty starting in the toddler age, refusal to use the potty for at least three periods of at least two weeks duration for at least a half year

Temper tantrums outbursts of rage that the parents were not able to con

trol, daily for long periods (at least two months) or during frequently recurring short periods (at least two weeks) for at least a half year during the toddler and preschool ages.

Stammering: child considered a stammerer by the parent. Child obviously bothered in school by stammering that caused him to avoid talking to strangers, at times prevented him from saying what he wished to say and was plainly embarassing to him, according to the parent's description. Occasional simple stuttering was thus not counted.

Secondary enuresis: after having been dependably dry for at least a half year the child during the preschool or school years (thus not as a toddler) wet himself day or night at least once a week during at least a half year.

Refusal to go to school: child had been so afraid to go to school that he had stayed home at least one day per week for at least two month-long periods.

Truancy without his parents knowledge and/or consent, child stayed away from school at least one whole day each week during at least two month-long periods.

Pilfering: behavior that the author regards as more serious in nature than petty pilfering, that is, outside the home, after having started school, of no petty value and on repeated occasions.

Frequent stomachache: at least three occasions of acute abdomen so severe that the parents at least considered seeking medical aid.

Frequent headache: child had had, according to the author's evaluation, severe headache at least once a week for at least two month-long periods for at least a half year and the parents had at least considered consulting a physician for this reason or on at least one occasion each month for at least a half year the child had been unable to remain in school because of headache.

An accident since the start of the investigation the accident should have caused symptoms or signs for a period of at least two weeks, or have meant an obvious danger to the child's life. Only accidents that occurred between January 1967 and midsummer 1968 were noted.

Mother mentally disturbed at the time of the interview (See page 67)

The reported tendency to consult a physician or seek hospital care: the average number of times the parent reported the one or the other for the illnesses and other situations sketched for the parents by the author (by heart from a written form)

Reported acute head injury: age at the time of head injury the nature of the accident, the place it occurred, supervision of the child at the time of the accident, the part of the head where the blow occurred, and whether the child was hospitalized. (For the first three variables the questions had the same formulations as in the questionnaire and the telephone interview.)

Since a few parents were willing to be interviewed at the hospital although the child in question refused to come to the hospital, the omissions for the parental interviews were somewhat fewer than for the clinical examination of the child. Of 371 possible, 346 or 93 %, were interviewed. The omissions were: for IH, 4 or 4 % for IO 14 or 8 %, for K, 7 or 7 %.

THE INTERVIEW WITH THE TEACHERS

The interviews with the teachers were carried out during the latter part of the spring of 1969 by a specially trained teacher with experience of such inter views from previous investigations at the Child Psychiatric Clinic in Umeå An interview with the child s teacher was held for 332 of a possible 371 children or for 90 % The omissions were. for IH 9 or 9 % for IO 18 or 10 % for K, 10 or 10 %

The opening question in the inter view with the teacher had a fixed for mulation and was Have there been any problems with the child at school?

When the interviewer judged from the teacher s reply that there had obviously been such problems, this was noted. When there had possibly been problems this was noted

The teacher s description of the pro blem(s) was recorded word for word as far as possible, to permit later evalua tion of whether the problem concerned learning, discipline or the child s gene ral behavior and adjustment in school

The following variables were further analysed

Child a problem in school problem with respect to learning, problem with respect to discipline, abnormal behavior in school

THE HOSPITAL RECORDS

The records of the child s reported hospitalizations were obtained succes sively and in batches during the fall of 1968 and the spring of 1969 and the author summarized the recorded ma terial in detail

In spite of repeated attempts to ob tain missing records there were a re markably large number of omissions. The records of hospital care for acute head injury were missing for 26 of 101 children in IH or for 26 %! The records of other hospital care for somatic con ditions were missing for 16 of 125 re ported admissions for IH or for 13 %, for IO 29 of 162, or 18 % and for K, 16 of 93 or 17 %

The reason for some of these omis sions would seem to be the fact that many Umeå Hospital records dis appeared without a trace when the in dividual clinic archives were transferred to a large central archive in the middle of the 1960' s

A large number of records of the children s births were also missing, although these records remained in the old Obstetrical Clinic archives. The numbers missing were for IH 15 or 15 % for IO 20, or 12 % for K, 13 or 13 %

On the basis of detailed summaries of the hospital records, including the records of delivery the author working continuously and without knowing to which group the child belonged selected the following variables for analysis

The number of admissions for acci dents or poisoning.

The number of admissions for prob lems for which an organic cause was established, and those for which such a cause was not established according to the author s evaluation

The mother s civil status at the time of delivery

The mother s age at the time of de livery

Reports in the obstetrical or hospital records of care for conditions which, in the author's opinion, have been shown by current diagnostic methods to carry a definite risk of brain injury (Acute postnatal head injuries and seizure states originating later in life were not included.)

From the records of acute head injuries, the following variables were selected.

Unconsciousness, vomiting or confusion associated with the head injury in question.

A diagnosis of cerebral concussion in the record of the head injury in question, based entirely on anamnestic data, as far as the author could judge.

During the spring and summer of 1968 all institutions for psychiatric care in the county where the child had resided were contacted for information as to whether the child or the parents were known to the institution, and, if this were the case, the record was requested. Detailed summaries were made of the childrens records obtained, briefer summaries of those of the parents.

The variables chosen for further analysis were the following:

The child had had psychiatric treatment as an out-patient or admitted to hospital.

The father had had psychiatric treatment. As above.

The mother had had psychiatric treatment. As above.

It is not possible to be sure how numerous the omissions were. Of the institutions to which inquiries were submitted regarding the children, 35 of 38, or 92 %, responded. Among 41 positive responses, two records were not obtainable.

Of the 58 institutions to which inquiries were submitted regarding the parents, 51, or 88 %, responded. Among 92 positive responses, three records were not obtainable.

The Umeå school dental records were obtained as photocopies. The omissions were for IH, 10 or 10 %; for IO 26, or 15 %; for K, 14 or 14 %

Two variables were analysed

Widespread caries. according to an experienced dentist's evaluation of the record.

Inadequate treatment due to lack of cooperation. according to an experienced dentist's evaluation of the record. (Missed dental appointment at least three times without cause.)

SOCIAL DATA IN VARIOUS ARCHIVES

The author collected all the records on the children and the parents that were to be found in the social temperance- and child welfare departments of the social welfare board of the city of Umeå Without knowing to which groups the children belonged, he briefly summarized the material thus obtained.

Similar data were gathered by telephone from the social welfare board in each community in which the child had at one time resided. A social worker was employed for this purpose. Only one community refused to answer this omission corresponded to less than one percent of the total children's years of life in the entire material.

The following variables were further analysed

Father known to temperance board

Mother known to *temperance board*

Family known to social welfare board

Sibling known to the temperance board or the child welfare board (The records were usually filed according to family regardless of the department concerned)

The child known to the child welfare board

Information was obtained from the tax authorities of the city of Umeå as to the father s and mother s tax declared incomes for the year 1967

The omissions were for IH 3 or 3 % for IO 5 or 3 % for K, 4 or 4 %

The following variables were further analysed

The family s declared income

The mother s declared income.

The children s school reports for the spring term of 1967 were obtained The omissions were for IH 6 or 6 %, for IO 20 or 12 % for K, 12, or 12 %.

The following variables were further analysed

The average grade, rounded to the *nearest whole number*

The grade in mathematics.

The grade in Swedish language.

The grade in physical education

The grade in crafts.

The grade in neatness.

The grade in behavior

Discussion of methods

MATERIAL

The author's reason for selecting for the child psychiatric section of the investigation all the children in the primary school population reported by questionnaire and in the subsequent telephone interview to have had an acute head injury associated with unconsciousness was twofold: First, it is clearly advantageous to work with populations when the methods used are uncertain and comparisons between the head injuries cared for in hospital and those cared for at home are complicated by the fact that the head injuries in these two groups were not of the same degree of severity. Secondly, it was necessary for practical reasons to limit the number of children to be investigated from the [illegible] in the original [illegible] population to about half this number. Head injury associated with unconsciousness provided a simple, concrete and easily defined criterion for accomplishing this and at the same time more sharply defined the range of severity of the head injuries, which was considered to be an advantage.

In retrospect it became apparent that any other procedure would have greatly decreased the value of the investigation (see the discussion of methods, epidemiologic section of the investigation). Namely, it became clear that only the occurrence of a concrete and dramatic primary cerebral symptom like unconsciousness could be reliably investigated retrospectively; this applied to both the head injuries cared for in hospital and those cared for at home.

However, not only were the head injuries in the investigated population cared for at home less severe than those in the investigated population cared for in hospital, but the former almost certainly included more irrelevant cases of trivial acute head injuries than the latter.

It is questionable to what extent each of the materials represents acute head injury associated with unconsciousness (see discussion of methods, epidemiologic section of the investigation), but the author believes that they are sufficiently representative for the purposes of the study. This is at least true of the investigated population cared for in hospital.

It seems reasonable to demand significance at the 0.1 level for a difference of [illegible] between the control material and an investigated population. To attain this, the author was forced to accept a large, unwieldy total material and, in addition, to ensure that the age and sex distributions in the control material were similar to those in the investigated population. This meant that comparisons of individual sex age groups became uncertain for the young-

The following variables were further analysed

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Family known to social welfare board

Sibling known to the temperance board or the child welfare board. (The records were usually filed according to family regardless of the department concerned.)

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Information was obtained from the tax authorities of the city of Umeå as to the father's and mother's tax-declared incomes for the year 1967

The omissions were: for IH 3 or 3 %, for IO 5 or 3 %, for K, 4 or 4 %

The following variables were further analysed

The family's declared income.

The mother's declared income.

The children's school reports for the spring term of 1967 were obtained. The omissions were: for IH, 6 or 6 %; for IO 20 or 12 %, for K, 12, or 12 %.

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The average grade, rounded to the nearest whole number

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er age groups, and that, for practical reasons, the methods used in the investigation had to be very rough if the investigation were to be carried out within a limited period of time. However the methods used are so imprecise by nature that this was hardly an additional disadvantage

METHODS

The author's evaluations of the psychic conditions of the children and their parents were unavoidably subjective However the mother and the child were evaluated on two fairly independent occasions and under quite different circumstances The correlation between the evaluations on the two occasions has been tested and is not impressive (PHI = 0 44 and 0 46 respectively) but it can be stated that the persons who were judged to be mentally disturbed on both occasions were usually clearly severely disturbed whereas those judged to be mentally disturbed on one or more occasions were probably more often misjudged

The interview method must be accepted as the uncertain method that it is Clinical research cannot be conducted without it (58) Unfortunately the extent of the investigation prevented the author from choosing the criteria for individual variables so that they would always correspond to the usual criteria in the literature. The information obtained by interview was not recorded in such a way as to permit better criteria to be constructed later

These limitations have several consequences

When the frequency of recurrent abdominal pain proved to be 29 % in the control material and the frequency of accidents between January 1 1967 and June 24 1968 proved to be 13 % for the control material it was obvious that these criteria were faulty and that the results are meaningless (5 12, 28)

In other cases the frequencies for the control material were low as for pilfering (1 %) truancy (1 %) enuresis (1 %) and mental illness of the father (6 %) or the mother (9 %) Review of the literature (16 18 35 36 37 45 46 57 62) shows that the criteria for pilfering and for mental illness were not especially severe and one must conclude that information as to these variables was withheld from the author to a greater extent than from other investigators. However the criteria for truancy and enuresis were more severe than those usually reported in the literature (16, 35 46 57 62, 67) and the frequencies found seem plausible in the light of the results of others

In general the frequencies in the control material for different variables treated in the interview with the parents are those expected or somewhat lower (4 7 13 35 36 37 47) In the interviews with the teachers the frequency of problem children in the control material was the same as that found in a previous investigation from the same clinic (20)

Convinced of the uncertainty of the method of retrospective interviewing, the author completely refrained from trying to evaluate possible previous psychic insufficiency in the child only concrete psychic symptoms can be treated with sufficient certainty

The author regards the old division into social groups as outmoded and not very meaningful. Instead, the family's income level, the breadwinner's educational level and the breadwinner's occupational status were evaluated. The classification of occupational status cannot be defined and merely reflects the author's subjective ranking of different occupations. The validity of this is open to question (1).

However, the author's rerating of the same occupational titles three months later corresponded fairly well with the original rating and also with independent ratings by a dentist and a lawyer and with the average ratings of a small number of persons chosen at random from the adult population at large (100).

The parents' answers to the author's little questionnaire as to what should have been done if the child had been ill in the various ways described cannot, of course, be taken as evidence of the parents' actual tendency to seek medical care for the child in different situations. On the other hand, it probably expresses the way the parents thought one ought to behave in different situations.

Archive data from various sources are always incomplete, but this is not as important in a statistical investigation as it would be in an analysis of individual cases. Such data are reliable in that they are not affected by methodology as are evaluations of physical and mental status and data obtained by interviewing.

However, the scope of the available information was so overwhelming that only simple rough variables could be analysed. The author was forced to clinically evaluate major parts of the summaries of the hospital records to arrive at important and clinically meaningful variables. These variables concerned the question whether an admission was motivated by a problem that proved to be of organic nature and whether perinatal or postnatal pathology described in the record carried a definite risk of brain damage. The consistency of the author's evaluations and the correlation between the author's evaluations and those of an experienced pediatrician were tested and found to be satisfactory.

Eleven families who had moved were traced, investigated clinically and interviewed at their new homes by the author, who then also carried out part of the psychological investigation. In four cases this was later completed by the school psychologist at the new place of residence. For the sake of simplicity these cases are not counted as omitted investigations "at the home" or "at the hospital".

GENERAL

It was possible to carry out the investigation in a satisfactory way. The omissions were disturbingly high only for the records of *reported* care of the children in hospital. There is, however, no reason to suppose that the results would have been *altered* in any important way had there been no omissions in this respect. This is also true for the *relatively* few omissions in the interviews with the teachers and for all the data from various archives.

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parents, the clinical examination of the child and the psychological investigation of the child were due to the families having moved from the city

The other half of the omissions represent children and/or parents who did not wish to take part in the investigation at the hospital and a few cases in which the parents refused to permit a home visit. In these cases there was probably a strong selective factor

However the cases that were omitted from investigation at the hospital presented the same frequencies of all the other variables, drawn from the home visit, the interviews with the teachers and the various archives, as the material as a whole. There is thus no reason to suppose that the results would have been different in any important way if these omissions could have been eliminated.

The blind technique that was used in the investigation at the hospital and for all the evaluations of data from other sources was preserved to a satisfactory extent.

The staggered sequence was observed to a satisfactory extent.

Results

THE PILOT STUDY PART OF THE QUESTIONNAIRE USED IN THE EPIDEMIOLOGIC SECTION OF THE INVESTIGATION

Except for the answer to the main question, the interpretation of the answers returned on the questionnaire was uncertain and tentative. This has already been discussed. However for the sake of completeness, these answers are summarized in Table 12. Since the materials are populations, evaluation of the differences in frequency of reported acute head injury does not require a calculation of significance.

It is obvious that children reported to have frequent headaches and children reported to have had other accidents were reported to have suffered acute head injuries more often than children in general.

Those in the populations who were reported to have had seizures and/or reading and writing difficulties appear to have suffered an acute head injury reported on questioning, which did not lead to hospital care, more often than other children. The importance that should be attributed to this finding and how it should be interpreted is not clear

Table 12. The frequency of acute head injuries cared for in hospital or at home reported by mailed questionnaire for the subdivisions of the primary school population defined by positive answers to items of pilot-study nature on the questionnaire.

	ACUTE HEAD INJURY REPORTED	
	Cared for in hospital	Cared for at home
Other accidents (266 children)	26 = 10 %	52 = 20 %
Seizures (185 children)	7 = 4 %	33 = 18 %
Headache (570 children)	58 = 10 %	91 = 25 %
Left-handedness (378 children)	16 = 4 %	47 = 12 %
Reading and writing problems (249 children)	12 = 5 %	40 = 16 %
In special class at school (304 children)	8 = 3 %	40 = 13 %
Had moved to Umeå (1466 children)	57 = 4 %	168 = 11 %
Other hospital care than for acute head injury (2179 children)	97 = 4 %	29 = 13 %
Entire primary school population (3105 children)	132 = 4 %	394 = 12 %

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Other accidents (266 children)	26 = 10 %	52 = 20 %
Seizures (185 children)	7 = 4 %	33 = 18 %
Headache (370 children)	38 = 10 %	91 = 25 %
Left-handedness (378 children)	16 = 4 %	47 = 1 %
Reading and writing problems (249 children)	12 = 5 %	40 = 16 %
In special class at school (304 children)	8 = 3 %	40 = 13 %
Had moved to Umeå (1466 children)	57 = 4 %	168 = 11 %
Other hospital care than for acute head injury (2179 children)	97 = 4 %	292 = 13 %
Entire primary school population (5103 children)	182 = 4 %	594 = 12 %

THE AUTHOR'S EVALUATIONS OF PSYCHIC CONDITIONS AND EMOTIONAL RELATIONSHIPS

These results are summarized in Table 13. The author found psychic insufficiency in the child and/or the mother more often in the investigated populations than in the control material. For the investigated population cared for in hospital the difference is significant at the 0.1 level both for the evaluation on home visit and for that at the hospital and for both the children and the mothers. The children in the investigated population cared for at home differed significantly from the control children with respect to the frequency of psychic insufficiency observed on home visit, the mothers of the investigated population cared for at home were significantly more often found to be psychically insufficient than the mothers of the investigated population cared for in hospital on home visit as well as at the hospital.

The foregoing discussion (page 62, 64, 67) made clear that it was not possible for the author to more precisely define the types of psychic insufficiency found

Table 13. The author's evaluation of the mental state of family members observed on home visit and at hospital and evaluation of the emotional relationships in the home.

	IH 101 children			IO 170 children			K 100 children		
	n	X	%	n	X	%	n	X	%
Child mentally disturbed									
on home visit	88	16	18 %	143	21	15 %	83	5	6 %
at hospital	95	28	29 %	154	32	21 %	90	13	14 %
on one occasion	97	34	35 %*	162	39	24 %	95	16	17 %
on both occasions	85	10	12 %	135	13	10 %	78	3	4 %
Mother mentally disturbed									
on home visit	94	19	20 %	156	42	27 %	90	10	11 %
at hospital	90	28	31 %	147	55	37 %	87	9	10 %
on one occasion	96	38	40 %*	160	62	39 %	92	18	20 %
on both occasions	87	10	11 %	146	29	20 %	85	5	6 %
Father mentally disturbed									
on home visit	67	8	12 %	114	16	14 %	70	7	10 %
Disturbed emotional climate									
on home visit	98	4	4 %	160	15	9 %	94	0	0 %

IH = investigated population cared for in hospital (101 children)
IO = investigated population cared for at home (170 children)
K = control material (100 children)
n = the number of children in a given group who were actually investigated
X = the number of positive findings of a given kind
* = significant difference in frequency between the respective head injury material and the control material (at the 0.1 level)

However, the mothers and children who were found to be psychically insufficient on both occasions had more markedly abnormal psychic traits than the mothers and children who were found to be psychically insufficient on only one of the two occasions. The variable Mentally disturbed on both occasions can therefore be interpreted as expressing more severe psychic disturbances. These were mainly found among the children in the investigated population cared for in hospital and among the mothers of the investigated population cared for at home.

On the other hand, the variable 'Mentally disturbed on one occasion better reflects the general incidence of milder degrees of psychic insufficiency but also includes more irrelevant cases of tension reactions to the situation and direct misjudgments than does the former variable. This makes no difference in regard to the children, but psychic insufficiency in the mother proves to be as common for the investigated population cared for in hospital as for the investigated population cared for at home.

The fact that psychic insufficiency in the father was not found to be more common in the investigated populations than in the control material does not mean that such was not actually the case, since there were many omissions and, in addition, the contact established with the fathers and the opportunities for observing them were less satisfactory throughout than for the mothers.

The fact that the emotional relationships between the parents or between the child and the parents were significantly more often considered to be disturbed in the investigated population cared for at home than in the control material (whereas the findings for the investigated population cared for in hospital were intermediate) would seem to be related to the fact that more severe psychic insufficiency in the mother was commonest in the investigated population cared for at home. The author namely attributed greater importance to the parents relationship to the child than to the reverse, and at the same time this evaluation was made with great restraint. Thus, in the control material there was not a single home in which the emotional relationships were judged to be disturbed.

THE PHYSICAL AND NEUROLOGICAL EXAMINATION OF THE CHILD

These results are summarized in Table 14 There were no significant differences between the three materials in regard to these variables. There was a nonsignificant higher incidence of signs of hemispheric damage in the investigated population cared for in hospital than in the control material, but the signs were usually very slight (unilateral positive Trömner or Babinski etc.) and the author would not attribute any importance whatever to these small differences.

In three cases there was definite, but by no means handicapping, hemiplegia two were in the investigated population cared for in hospital and one in that cared for at home. However no conclusions whatever can be drawn from these few cases.

Table 14 The author's findings on physical examination and neurological investigation of the child at hospital.

	IH 101 children			IO 170 children			K 100 children		
	n	x	%	n	x	%	n	x	%
Unusually tall	94	4	4 %	152	6	4 %	89	6	7 %
Unusually short	94	1	1 %	152	1	1 %	89	2	%
Overweight	94	7	7 %	152	4	3 %	89	3	3 %
Pubertal development	94	51	54 %	152	87	57 %	89	49	55 %
Dysplasias	94	4	4 %	152	6	4 %	89	2	2 %
Upper respiratory infection	94	8	9 %	152	8	5 %	89	2	2 %
Poor finger dexterity	94	11	12 %	152	18	12 %	89	12	13 %
Good finger dexterity	94	4	4 %	152	16	11 %	89	7	8 %
Poor general motor coordination	94	21	22 %	152	26	17 %	89	17	19 %
Good general motor coordination	94	3	3 %	152	12	8 %	89	7	8 %
Left-handed or ambidextrous	94	11	12 %	152	7	18 %	89	12	13 %
Slight signs of past hemispheric damage	94	8	9 %	15	9	6 %	89	2	2 %
Convergence insufficiency (20 cm) and/or loss of cranial nerve function	94	10	11 %	152	14	9 %	89	7	8 %

For explanation of the symbols, see table 13

In seven cases there was a suspicion of brain damage, based on the findings in the child psychiatric examination but there was no difference between the groups (IH 2, IO 2, K 3)

THE INTERVIEW WITH THE PARENTS AT THE HOSPITAL

As is shown in Table 15 the three materials did not differ with respect to the family income levels Although there were no significant differences in educational and occupational levels (according to the author's subjective evaluation) between the head injury material and the control material there were clear differences with respect to these variables between the investigated population cared for in hospital and that cared for at home Comparison of these groups shows that the breadwinners for the investigated population cared for in hospital tended to have low status, and the breadwinners for the investigated population cared for at home to have high status.

The implications of this are not clear but the findings could reflect the same cultural differences that lead to a child with an acute head injury of a certain degree of severity being cared for in hospital in one case but not in the other One complicating factor is the possibility that well-educated parents remembered and reported moderately severe acute head injuries more often than other parents Were this so the difference in what the two investigated

Table 15 The family's social status in terms of 1) Occupational status (5-point scale, 1 = highest) according to the author's subjective evaluation, 2) Educational level (5-point scale, 1 = highest) 3) Income level according to the parents' tax-declared income for the year 1967

		IH 101 children			IO 170 children			K 100 children		
			X	%	n	X	%		X	%
Occupational status	1	97	7	7 %	155	19	12 %	93	12	13 %
	2	97	12	12 %	155	29	19 %	93	11	12 %
	3	97	17	18 %	155	32	21 %	93	21	23 %
	4	97	27	28 %	155	38	25 %	93	21	23 %
	5	97	34	35 %	155	37	24 %	93	28	30 %
Educational level	1	97	10	10 %	155	31	20 %	93	15	16 %
	2	97	12	12 %	155	27	17 %	93	14	15 %
	3	97	10	10 %	155	12	8 %	93	5	5 %
	4	97	27	28 %	155	45	29 %	93	23	25 %
	5	97	38	39 %	155	40	26 %	93	36	39 %
Income level Sw cr	50,000 or more	97	10	10 %	165	22	13 %	96	10	10 %
	30 000—49 999	97	33	34 %	165	50	30 %	96	30	31 %
	20 000—29 999	97	27	28 %	165	48	29 %	96	29	30 %
	10 000—19 999	97	18	19 %	165	33	20 %	96	17	18 %
	Less than 9 999	97	9	9 %	165	12	7 %	96	10	10 %

For explanation of the symbols, see table 13
One U $ dollar is worth approximately 5 Sw cr one English pound approximately 12 Sw cr.

populations actually represent would be greater than the author supposed and discussed in the discussion of methods, epidemiologic section of the investigation. However the risk that this was so is believed to be slight.

The results with respect to various socio-medical variables and a number of environmental factors that could possibly put a strain on a child are summarized in Table 16

The investigated population cared for in hospital differs significantly from the control material in the following respects The mother had more often given birth to the child before the age of 21 the mother had been unmarried, divorced or widowed during some period in the child's life more often than in the control material, the mother had worked outside the home at least half time for at least a period of three years before the child started school more often than in the control material the father had more often been mentally ill, with recurrent or prolonged periods of being unable to work during some period in the child's life.

The investigated population cared for at home falls between the population cared for in hospital and the control material with respect to the mother's age at the child's birth and her working outside the home before the child started

Table 14 The author's findings on physical examination and neurological investigation of the child at hospital

	IH 101 children			IO 170 children			K 100 children		
	n	X	%	n	X	%	n	X	%
Unusually tall	94	4	4%	152	6	4%	89	6	7%
Unusually short	94	1	1%	152	1	1%	89	2	2%
Overweight	94	7	7%	152	4	3%	89	3	3%
Pubertal development	94	51	54%	152	87	57%	89	49	55%
Dysplasias	94	4	4%	152	6	4%	89	2	2%
Upper respiratory infection	94	8	9%	152	8	5%	89	2	2%
Poor finger dexterity	94	11	12%	152	18	12%	89	12	13%
Good finger dexterity	94	4	4%	152	16	11%	89	7	8%
Poor general motor coordination	94	21	22%	152	26	17%	89	17	19%
Good general motor coordination	94	3	3%	152	12	8%	89	7	8%
Left handed or ambidextrous	94	11	12%	152	27	18%	89	12	13%
Slight signs of past hemispheric damage	94	8	9%	152	9	6%	89	2	2%
Convergence insufficiency (20 cm) and/or loss of cranial nerve function	94	10	11%	152	14	9%	89	7	8%

For explanation of the symbols, see table 13

In seven cases there was a suspicion of brain damage, based on the findings in the child psychiatric examination but there was no difference between the groups (IH 2, IO 2, K 3)

THE INTERVIEW WITH THE PARENTS AT THE HOSPITAL

As is shown in Table 15 the three materials did not differ with respect to the family income levels. Although there were no significant differences in educational and occupational levels (according to the author's subjective evaluation) between the head injury material and the control material there were clear differences with respect to these variables between the investigated population cared for in hospital and that cared for at home Comparison of these groups shows that the breadwinners for the investigated population cared for in hospital tended to have low status, and the breadwinners for the investigated population cared for at home to have high status

The implications of this are not clear but the findings could reflect the same cultural differences that lead to a child with an acute head injury of a certain degree of severity being cared for in hospital in one case but not in the other One complicating factor is the possibility that well-educated parents remembered and reported moderately severe acute head injuries more often than other parents Were this so the difference in what the two investigated

younger mothers to regard an acute head injury of a moderate degree of severity as trifling, and are thus more likely to seek hospital care for such an injury In practical clinical experience one often gets the impression that this is the case.

It can be mentioned that the above age difference is reflected in the mothers age distribution. for the investigated population cared for at home only 12 % of the mothers were born before 1921 and as many as 35 % after 1930, compared with 22 % and 27 % respectively in both the other materials.

There was no difference in the fathers age distribution in the three materials.

In summary the interview investigation of the milieus in which the children were raised indicates that for both the investigated populations this was more often characterized by psychic insufficiency in the parents (the father in IH, the mother in IO) and other factors that could possibly put a strain on a child (a very young mother an incomplete home, a mother who early worked outside the home) than was the case for the control material. These circumstances are more marked for the investigated population cared for in hospital, for which they are significant at the 0 1 level. Even such factors as physical illness of the parents, repeated total changes of the child s environment and frequent changes of the person caring for the child during the toddler or preschool years tended to be more frequent in the investigated populations.

It may well be that parents recall a past slight head injury in a child more often when there are fewer siblings than when there are many siblings. This may explain the low but not significantly lower frequency of four or more siblings in the families of IO compared with the control families.

Table 17 summarizes the interview findings with respect to development, psychic symptoms and seizures in the child.

The accidents the children suffered during the period January 1 1967 — June 24 1968 are also included, but they show no differences between the materials. This has very little importance as the author included all reported minor accidents, and the criterion for the variable Accidents with injury was merely that the accident led to subjective difficulty for a period of two weeks or that there was objectively verifiable injury at the time of the accident or that the child's life was clearly in danger The meaning of positive or negative responses to this variable is very uncertain and the responses perhaps reflect more the attitudes of the mothers than the number of minor accidents that actually occurred.

The investigated population cared for in hospital differs significantly from the control material in the following respects The child had more often had primary or secondary enuresis, the child had more often been truant from school or engaged in rather serious pilfering, and the child had more often had severe headaches For almost all the other variables there is no difference or only a negligible difference from the control material.

The investigated population cared for at home is in an intermediate position

Table 16. The child's home environment as revealed by answers to questions in the interview with the parents. (The mother's age and civil status at the time of delivery were, however taken from the obstetrical record in most cases, and moved to Umeå or not moved from earlier interviews or from the questionnaire)

	IH 101 children			IO 170 children			K 100 children		
	n	X	%	n	X	%	n	X	%
Mother's age at delivery									
— a minor (20 years or younger)	100	12	12 %	169	15	9 %	100	4	4 %
— 35 years or older	100	17	17 %	169	8	5 %*	100	15	15 %
Incomplete home during some period in the child's life	96	23	24 %*	156	21	13 %	91	11	12 %
The child is an only child	96	5	5 %	156	8	5 %	91	8	9 %
eldest	96	31	32 %	156	75	48 %	91	35	38 %
youngest	96	29	30 %	156	39	25 %	91	25	27 %
a middle child	96	31	32 %	156	34	22 %	91	23	25 %
The child is one of at least 4 siblings	96	27	28 %	155	25	16 %	91	23	25 %
Siblings closely spaced (at least 3 children under 5 years of age at one time)	96	15	16 %	156	23	15 %	92	19	21 %
Mother worked outside the home before child started school	97	41	42 %	156	54	35 %	93	25	27 %
Frequent changes of person caring for child before child started school	97	8	8 %	156	12	8 %	93	3	3 %
At least 3 complete changes of environment i the child's life	97	21	22 %	155	39	25 %	93	18	19 %
Moved from a town	100	17	17 %	167	47	28 %	97	21	22 %
from a rural area	100	22	22 %	167	33	20 %	97	25	26 %
Had not moved	100	61	61 %	167	87	52 %	97	51	53 %
During child's life father has been									
physically ill	83	16	19 %	152	32	21 %	86	15	17 %
mentally ill	83	15	18 %	152	9	6 %	86	5	6 %
During child's life mother has been									
physically ill	97	22	23 %	156	28	18 %	93	15	16 %
mentally ill	97	9	9 %	156	29	19 %	93	8	9 %

For explanation of the symbols, see table 13

school but in the other respects mentioned above it does not differ from the control material. On the other hand, the investigated population cared for at home — unlike the investigated population cared for in hospital — differs from the control material in that the mother was *seldom 35 years old or* older when the child was born and in that the mother more often reported having had her own psychic problems which had led to recurrent or prolonged periods of being unable to work during some period in the child's life.

The fact that the mothers of the investigated population cared for at home were seldom 35 years old or older when *the child was born* can be explained most simply by the following hypothesis. Older mothers are less likely than

It may also be that early motor development is disproportional to the child's general development and could thus mean a greater likelihood of the child's incurring an acute head injury. Infants and toddlers are better represented in the investigated population cared for at home than in that cared for in hospital, and this could well explain the higher frequency of early walking in the former material. The author however is sceptical of this and other possible explanations and tends to interpret this difference as an irrelevant expression of the uncertainty of the information obtained.

On the other hand, the excess frequency of seizure states in the population cared for at home demands an explanation. The difference is large (15% compared with 3% in the control material) and is not due to fainting, which was reported in only a few cases. Affect convulsions, febrile convulsions and overt epilepsy predominate in equal proportions and were reported in the same relative proportions within each of the three materials. In only one case did the author judge, on the basis of the parental interview, that there had been no acute head injury of a sufficient degree of severity but that the child had been included in the investigation because the parents had misinterpreted affect convulsions as a primary cerebral symptom associated with head injury and had reported this in the telephone interview.

Nonetheless, it is tempting to interpret the excess frequency of seizure states in the investigated population cared for at home as a reflection of the fact that it is very difficult to retrospectively distinguish children who struck their heads in a seizure from children who suffered a severe blow to the head and had a cerebral concussion. For many of the cases cared for in hospital, this differential diagnosis may have been made by the physician in charge at the time, which may explain why there is no definite excess frequency in the investigated population cared for in hospital. The parents, namely, knew that it was not a case of cerebral concussion and therefore gave a negative answer to the main question on the questionnaire.

However, during the telephone interview work the author did not find this to be a difficult differential diagnosis; only a few children in the head injury population were believed to have had a seizure instead of an acute head injury, and there were only a few cases in which convulsions were reported as the primary cerebral symptom.

Other possible explanations would seem to be far fetched, and the author tends to regard the situation as outlined above.

This would mean that about ten or twenty children with seizure states were erroneously included in the investigated population cared for at home. It is hard to believe that this would seriously affect the results of the investigation.

In regard to the child's development and psychic symptoms, the results of the interview investigation indicate that there are no important differences between either of the investigated populations and the control material with respect to the children's general development (with the possible exception of early motor development), but that the

Table 17 The picture provided by answers to questions in the parental interview of the children's development, symptoms of infant neurosis, behaviour disorders, other mental symptoms, accidents since the start of the investigation, and seizure states involving at least three episodes of grand mal, atypical epileptic seizures, febrile convulsions, affect convulsions or fainting

	IH			*IO*			K		
	101 children			170 children			100 children		
	n	X	%	n	X	%	n	X	%
Walked without support									
before 11 months of age	97	19	20 %	156	37	4 ⌐	93	12	13 %
after 17 months of age	97	2	2 ⌐	156	4	3 ⌐	93	4	4 %
Spoke two-word sentences									
before 1½ years of age	97	7	7 %	156	17	11 %	93	8	9 %
after 2½ years of age	97	9	9 %	156	16	10 ⌐	93	7	8 %
Failed the school maturity test	97	9	9 ⌐	156	15	10 %	93	8	9 %
Refused to eat when small	97	9	9 %	156	1	8 ⌐	93	6	6 %
Was afraid of the potty when small	97	4	4 ⌐	156	5	3 %	93	4	4 %
Had temper tantrums when small	97	7	7 ⌐	156	13	8 ⌐	93	3	3 %
Left sidedness	97	8	8 %	156	15	10 ⌐	93	7	8 %
Stammering in school	97	3	3 %	156	4	3 %	93	2	2 %
Primary enuresis when of school age	97	7	7 %	156	11	7 %	93	1	1 %
Secondary enuresis	97	7	7 %	156	7	4 %	93	0	0 %
Refusal to go to school	97	11	11 %	156	14	9 %	93	6	6 %
Truancy	97	7	7 %	156	5	3 %	93	1	1 ⌐
Repeated pilfering	97	10	10 %	156	12	8 ⌐	93	1	1 %
Frequent stomachache	97	37	38 %	156	46	30 %	93	7	29 ⌐
Frequent headache	97	30	31 ⌐	156	36	23 %	93	8	9 %
Reported accidents									
— all	97	17	18 %	156	38	24 ⌐	93	21	23 %
— those with some injury	97	7	7 %	156	3	15 ⌐	93	12	13 %
Seizures	97	7	7 %	156	23	15 %	93	5	5 %

For explanation of the symbols, see table 13

with respect to the above variables and differs significantly from the control material with respect to both primary and secondary enuresis and headache — *but not with respect to truancy*

In addition it was significantly more often reported for the investigated population cared for at home than for the control material that the child could walk without support before the age of 11 months and that the child had had at least three seizures of grand mal type, atypical epilepsy febrile convulsions, affect convulsions or simple fainting

In both the above *respects* the investigated population cared for in hospital *is in an intermediate position*

The reliability of this information is surely very poor at least in regard to the ability to walk early and the apparently significant difference between the groups with respect to both variables may perhaps be due to chance and the true *differences* may be irrelevant.

so unproven that one cannot on this basis exclude cultural differences between the materials with respect to attitudes toward different levels of medical assistance in various situations.

THE PSYCHOLOGICAL INVESTIGATION

The results of psychological testing are given in Table 18. There were no significant differences between the control material and either of the investigated populations, and no important differences between the investigated populations. It should perhaps be noted that the children in the investigated population cared for in hospital had fewer below-average performances on the verbal component test from WIT than did the children in the other materials. This difference is nearly significant but does not correspond to a general trend. The meaning of this is unclear and hard to explain. The author regards it as an irrelevant difference due to chance.

A review of the test results shows that there were the same levels of intelligence, the same evidence of traits associated with brain lesions, and the same evidence of reading and writing difficulties in the different materials.

Of course this does not mean that brain damage or reading and writing difficulties could not be present in excess frequency in one or both of the investigated populations, since a retrospective procedure using the methods now current could possibly allow many cases to slip by unnoticed. However there is no positive evidence for such excess frequencies.

SCHOOL GRADES AND THE INTERVIEW WITH THE TEACHERS

There were no significant differences between the three materials in regard to school performance, skill at crafts and gymnastics, grades for neatness and behavior or the teacher's report as to whether the child was a problem in school, either in general or with respect to learning, discipline or general behavior (See Table 19.)

THE DATA FROM VARIOUS ARCHIVES

The results of the review of the social welfare archives, the hospital archives and the school dental archives are given in Table 20.

Families known to the social welfare board through having received social aid at some time during the child's life were significantly more frequent for both the investigated populations than in the control material.

There is a slightly greater tendency for both the mother and the father to have been studied and/or treated at a psychiatric institution in the investigated population cared for in hospital than in the control material, and the children showed the same slight and non-significant tendency to have been hospitalized for difficulties that could not with certainty be traced to organic causes.

On the other hand, the child had been the subject of psychiatric study or treatment significantly more often in the investigated population cared for

special defect in development represented by primary enuresis, and various psychic symptoms such as secondary enuresis, truancy, pilfering and headache are far more common in both the investigated populations (somewhat more predominant in the investigated population cared for in hospital) than in the control material.

Analysis of the parents' reports as to whether they in certain situations, would seek help for their child from a physician, at a hospital, from the district nurse or from other medical personnel showed no difference between the materials. The questions were posed in such a way that the answers would represent the parent's concept of how and when there may be a need for medical assistance in various common situations involving children. However the method is so uncertain and its value

Table 18. Results of psychological tests.

	1H			1O			K		
	101 children			170 children			100 children		
	n	X	%	n	X	%	n	X	%
Result on the verbal part of WIT									
above average	93	16	17 %	154	29	19 ⌐	91	15	16 %
below average	93	15	16 ⌐	154	40	6 %	91	[illegible]6	29 ⌐
Result on the spatial part of WIT									
above average	93	20	22 %	154	33	21 %	91	14	15 %
below average	93	23	25 %	154	38	25 %	91	24	26 ⌐
Better verbally than spatially									
3 stanine points	93	3	3 %	154	11	7 %	91	8	9 %
4 stanine points	93	3	3 %	154	10	6 %	91	2	2 %
5 stanine points or more	93	2	2 %	154	1	1 %	91	0	0 ⌐
Better spatially than verbally									
3 stanine points	93	7	8 %	154	11	7 %	91	8	9 %
4 stanine points	93	4	4 %	154	6	4 %	91	2	2 %
5 stanine points or more	93	2	2 %	154	3	2 %	91	1	1 %
Result on the block pattern test from WISC									
above average	91	7	8 %	154	9	6 ⌐	91	2	2 %
below average	91	29	32 %	154	42	7 %	91	31	34 %
Result on dictation test from DLS									
above average	91	15	16 %	149	33	22 %	85	12	14 %
below average	91	19	21 ⌐	149	45	30 %	85	24	28 %
Result on comprehension test from DLS									
above average	86	18	21 ⌐	137	26	19 %	74	11	15 %
below average	86	17	20 %	137	32	23 ⌐	74	16	22 %
Observations									
Uncooperative	91	13	14 %	151	16	11 %	85	10	1[illegible] %
Difficulty in concentrating	91	18	20 %	151	23	15 %	85	16	19 %

For explanation of the symbols, see table 13

Table 20 Findings on reviewing data in various archives

	IH 101 children			IO 170 children			K 100 children		
		X	%		X	%		X	%
Father known to psychiatric clinic	88	14	16 %	150	12	8 %	91	8	9 %
Mother known to psychiatric clinic	99	18	18 %	168	27	16 %	99	13	13 %
Child known to child psychiatric clinic	101	18	18 %	170	18	11 %	100	3	3 %
Child hospitalized for accident or poisoning	101	16	16 %	170	12	7 %	100	3	3 %
Number of hospitalizations for conditions of									
established organic origin	101	56	56 %	170	49	29 %	100	39	39 %
unestablished origin	101	22	22 %	170	27	16 %	100	16	16 %
Child hospitalized or treated in the obstetrical department for conditions carrying definite risk of brain damage (excluding the head injury under study) (author' evaluation)	101	8	8 %	170	15	9 %	100	6	6 %
Widespread caries according to the school dental records	91	30	33 %	144	49	34 %	86	27	31 %
Missed school dental appointment at least three times without cause	91	6	7 %	144	17	12 %	86	7	8 %
Family known to social welfare board	101	13	13 %	170	19	11 %	100	3	3 %
Sibling known to temperance board or child welfare board	96	4	4 %	162	8	5 %	92	5	5 %
Father known to temperance board	88	8	9 %	150	9	6 %	91	3	3 %
Mother known to temperance board	99	1	1 %	168	2	1 %	99	1	1 %
Child known to child welfare board	101	13	13 %	170	18	11 %	100	11	11 %

For explanation of the symbols, see table 15

tigated population cared for in hospital — than in the control material.

In addition, the children in the investigated population cared for in hospital had previously been hospitalized for an accident other than the head injury in question or for poisoning significantly more often than the children in the control material.

SUMMARY

The results of a broad child psychiatric survey thus clearly show that a child reported to have been cared for in hospital for an acute head injury associated with unconsciousness was more likely than a control child to exhibit various psychic symptoms of so-called stress type (enuresis, truancy pilfering, headache) was more likely to have been in contact with a child psychiatric clinic and was more often judged to suffer from psychic insufficiency on examination later in life.

Children reported to have had an acute head injury associated with unconsciousness but cared for at home tend to differ from the control children in all these respects, but the difference is often not significant.

For the investigated population cared for at home, there were reports of early motor development and of seizures

Table 19 Findings on reviewing the school reports for spring 1967 and from interview with the teachers spring 1969

		IH 101 children			IO 170 children			K 100 children		
		n	X	%	n	X	%	n	X	%
Average grade[1]	1	93	4	4 %	150	4	3 %	88	1	1 %
	2	95	14	15 %	150	28	19 %	88	13	15 %
	4	93	23	24 %	150	35	23 %	88	26	30 %
	5	95	4	4 %	150	6	4 %	88	1	1 %
Swedish language[2]	1	95	6	6 %	150	7	5 %	88	1	1 %
	2	95	17	18 %	150	27	18 %	88	17	19 %
	4	95	21	22 %	150	37	5 %	88	23	26 %
	5	95	5	5 %	150	17	11 %	88	8	9 %
Mathematics	1	94	6	6 %	148	10	7 %	88	2	2 %
	2	94	26	28 %	148	34	23 %	88	16	18 %
	4	94	23	24 %	148	38	26 %	88	27	31 %
	5	94	7	7 %	148	13	9 %	88	9	10 %
Physical education	1	94	7	7 %	149	6	4 %	88	6	7 %
	2	94	12	13 %	149	25	17 %	88	19	22 %
	4	94	26	28 %	149	36	4 %	88	29	33 %
	5	94	5	5 %	149	8	5 %	88	3	3 %
Crafts	1	84	3	4 %	125	4	3 %	76	2	3 %
	2	84	13	15 %	125	25	20 %	76	11	14 %
	4	84	19	23 %	125	29	23 %	76	25	33 %
	5	84	6	7 %	125	7	6 %	76	3	4 %
Grade 1 or 2 for neatness		71	4	6 %	115	6	5 %	64	4	6 %
Grade 1 or 2 for behaviour		71	4	6 %	115	6	5 %	64	4	6 %
Problem child in school		92	8	9 %	152	16	11 %	90	9	10 %
Problem with respect to:										
learning		9	4	4 %	152	7	5 %	90	5	6 %
discipline		92	6	7 %	152	12	8 %	90	4	4 %
general behaviour		92	7	8 %	152	9	6 %	90	7	8 %

[1] For explanation of the symbols, see table 13

[2] The grading system in Swedish primary schools is based on a 5-point scale with 5 highest

in hospital than in the control material whereas the investigated population cared for at home was intermediate in this respect. The distribution of different types of referrals and of different types of psychic difficulties was the same in each of the materials.

In summary even the data obtained from various archives indicated that there were more stressful circumstances in the children's environments and that the children themselves exhibited psychic symptoms more often in the head injury materials — mainly in the inves

Table 20 Findings on reviewing data in various archives.

	IH 101 children			IO 170 children			K 100 children		
		X	%		X	%		X	%
Father known to psychiatric clinic	88	14	16 %	150	12	8 %	91	8	9 %
Mother known to psychiatric clinic	99	18	18 %	168	27	16 %	99	13	13 %
Child known to child psychiatric clinic	101	18	18 %	170	18	11 %	100	3	3 %
Child hospitalized for accident or poisoning	101	16	16 %	170	12	7 %	100	3	3 %
Number of hospitalizations for conditions of									
established organic origin	101	36	36 %	170	49	29 %	100	39	39 %
unestablished origin	101	22	22 %	170	27	16 %	100	16	16 %
Child hospitalized or treated in the obstetrical department for conditions carrying a definite risk of brain damage (excluding the head injury under study) (author evaluation)	101	8	8 %	170	15	9 %	100	6	6 %
Widespread caries according to the school dental records	91	30	33 %	144	49	34 %	86	27	31 %
Missed school dental appointment at least three times without cause	91	6	7 %	144	17	12 %	86	7	8 %
Family known to social welfare board	101	13	13 %	170	19	11 %	100	5	5 %
Sibling known to temperance board or child welfare board	96	4	4 %	162	8	5 %	92	5	5 %
Father known to temperance board	88	8	9 %	150	9	6 %	91	3	3 %
Mother known to temperance board	99	1	1 %	168	2	1 %	99	1	1 %
Child known to child welfare board	101	13	13 %	170	18	11 %	100	11	11 %

For explanation of the symbols, see table 13.

tigated population cared for in hospital — than in the control material.

In addition, the children in the investigated population cared for in hospital had previously been hospitalized for an accident other than the head injury in question or for poisoning significantly more often than the children in the control material.

SUMMARY

The results of a broad child psychiatric survey thus clearly show that a child reported to have been cared for in hospital for an acute head injury associated with unconsciousness was more likely than a control child to exhibit various psychic symptoms of so-called stress type (enuresis, truancy pilfering headache) was more likely to have been in contact with a child psychiatric clinic and was more often judged to suffer from psychic insufficiency on examination later in life.

Children reported to have had an acute head injury associated with unconsciousness but cared for at home tend to differ from the control children in all these respects, but the difference is often not significant.

For the investigated population cared for at home, there were reports of early motor development and of seizures

more often than in the control material These differences are hard to evaluate but the author believes that they are due either to chance, to defects in the method or to the population s not being representative of acute head in juries of the reported degrees of sever ity that actually occurred

Using the routine neurological child psychiatric and psychological methods currently used for the diagnosis of brain damage no differences could be detect ed between either of the head injury materials and the control material

In sharp contrast there were many significant differences mainly between the investigated population cared for in hospital and the control material but also between the latter and the inves tigated population cared for at home, with respect to circumstances that can be regarded as indicative of constitu tional or environmental causes of the psychic problems found among the children Thus for the head injury materials, the mothers had more often been very young at the time of delivery there had more often been an incom- plete home during the child s life there had more often been a need for social welfare assistance etc But above all, the parents had more often suffered from psychic insufficiency during the child s life and this was confirmed for the mothers who were more often judged to be mentally disturbed at the time of the investigation

The fact that psychic symptoms and an unfavorable milieu characterize chil- dren reported to have had cerebral con cussion cared for at home as well as those cared for in hospital is evidence against the hypothesis that such factors are responsible for hospitalization of the head injured child

It should also be noted that children in the investigated population cared for in hospital had previously been hospital ized for an accident other than the head injury in question or for poison ing far more often than the children in the control material

Discussion of results

The value of the results depends in part on whether the materials were representative, and in part on the dependability of the methods — both have been discussed at length in earlier parts of the work.

An analysis of the results can give an indication of the reliability of the methods used for the individual variables and even of the degrees to which the materials were representative.

Table 21 shows the percentage frequencies in different sex and age groups of those variables that differentiate the investigated populations, cared for at home and in hospital respectively from the controls. Note that there is a positive correlation between IH and/or IO and the variable in question in all cases except that of the mother having been 35 or older at the time of delivery Surprisingly it can be shown that this variable shows a significant positive covariation with the variables Incomplete home and 'Father mentally ill' in the entire material. Possibly children of older mothers suffer head injuries less often than other children and, if injured, are more likely to be hospitalized.

The difference between the investigated population cared for in hospital and the control material with respect to 'Father mentally ill' is entirely due to the high frequency of this variable for older boys in IH It is difficult to see why this should be so it may be taken as a warning that there may be some uncertainty in this result.

It is not surprising that pilfering was reported mainly for the older boys in the investigated populations, but with respect to the variables 'Primary enuresis and Child (judged to be) disturbed on both occasions one finds the expected predominance of boys only in the investigated population cared for in hospital, whereas in the investigated population cared for at home the differences from the control material for these two variables are due to the high frequencies for girls.

The author would not venture to try to explain this, and this observation casts uncertainty over the value of these results. The same is true of the fact that Repeated seizures was reported mainly for girls in both the investigated populations although there was no reason to expect a sex difference in this respect.

However there are no other peculiar age or sex distributions for the other variables in Table 21 and in evaluating the findings mentioned above it should be borne in mind that the age and sex groups in the material are small (from 24 to 99 children) The author does not consider that the findings discussed above cast doubt on the results

more often than in the control material These differences are hard to evaluate, but the author believes that they are due either to chance, to defects in the method or to the population's not being representative of acute head injuries of the reported degrees of severity that actually occurred

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The fact that psychic symptoms and an unfavorable milieu characterize children reported to have had cerebral concussion cared for at home as well as those cared for in hospital is evidence *against the hypothesis that such factors* are responsible for hospitalization of the head injured child

It should also be noted that children in the investigated population cared for in hospital had previously been hospitalized for an accident other than the head injury in question or for poisoning far more often than the children in the control material

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T bl 21 Percentage frequency n d fferent sex and age groups of those variables th t d fferentiate the invest gated groups from the controls

	Born			IH		Born			IO		Born			K	
	After 1956	1954—1956	Before 1954	Boys	Girls	After 1956	1954—1956	Before 1954	Boys	Girls	After 1956	1954—1956	Before 1954	Boys	Girls
Mother minor at delivery	4	14	14	14	10	9	8	9	8	10	3	7	2	2	8
Mother 35 or older at delivery	8	20	20	16	19	2	0	5	4	6	17	30	5	14	18
Incomplete home in child' life	13	12	20	16	15	4	23	7	10	9	7	4	10	6	8
Mother worked early in child's life	46	50	31	45	38	32	37	35	33	36	29	28	25	28	25
Mother s ncome 5 000 — Sw cr or more	64	62	57	55	68	48	41	39	34	46	31	40	46	36	47
Family known to social welfare board	21	9	1	15	10	9	8	14	11	11	7	4	5	5	5
Emotionally disturbed home (on home visit)	4	6	2	5	3	4	11	12	9	9	0	0	0	0	0
Father mentally ill (nterview)	14	12	23	25	6	4	7	5	6	7	4	9	6	6	6
Mother mentally ill (nterview)	4	9	12	10	8	18	20	18	21	15	11	12	5	9	7
Mother disturbed (both occasions)	13	12	7	13	8	16	19	19	20	15	14	4	0	4	8
Mother disturbed (one or more occasions)	44	33	42	39	47	33	39	45	45	34	25	17	17	21	18
Child walked early	13	16	27	23	15	19	23	27	22	26	11	12	15	13	13
Primary enuresis, school age	4	9	7	12	0	4	9	8	8	6	0	0	3	2	0
Secondary enuresis	8	3	7	9	5	4	9	3	7	2	0	0	0	0	0
Truancy	8	3	10	9	5	0	3	5	2	5	0	0	3	0	3
Repeated pilfering	4	3	20	17	0		6	12	12	2	0	0	3	2	0
Frequent headache	20	27	39	29	33	8	23	33	19	29	0	12	13	10	8
Hospitalized f r accident (other)	16	20	12	20	9	9	8	11	6	9	0	0	7	2	5
Repeated seizures	4	9	7	5	10	15	17	13	12	18	4	0	5	5	0
Child psychiatric contact	4	23	21	20	14		3	20	11	10	3	0	9	8	0
Child disturbed (both occasions)	10	11	13	18	3	12	12	7	9	11	5	5	3	5	3
Child disturbed (on or more occasions)	42	21	30	39	30	30	19	18	24	25	18	15	12	18	15

F r explanation of the symbols, see tabl 13

The positive co-variations in the total material between different variables important for the results of the investigation have been compiled in Table 22.

It is clear from the table how mutually interrelated the variables are that, by their high frequencies in IH and/or IO differentiate the investigated populations from the control material.

Only the variable 'Hospitalized for accident before 1967' is not correlated to another individual variable important for the overall result. The correlation of the mother's having a declared income of 5000- or more only to the evaluation of the mother as disturbed on both occasions of observation is surprising and hard to understand

The variable Child walked early is correlated only to the variable Primary enuresis which is also surprising and hard to understand

The variable Mother a minor at delivery' is also correlated to only one variable, namely pilfering. The perhaps somewhat far fetched explanation of this connection might be that very young mothers more often have emotionally starved children, who are more likely than other children to pilfer Mainly however it is surprising and hard to understand.

However Table 22 as a whole confirms the interrelationship of intrinsic and environmental factors affecting the child that have been found in general clinical experience to be related. The author regards this as supporting the value of the results of the investigation in general, especially since the information on the child was obtained in quite different ways and from different sources for those variables that did not stem directly from the interviews with the parents.

The author considers that the results of the investigation demonstrate beyond doubt that a general picture of unfavorable environmental conditions, psychically insufficient parents, and behavioral disturbances and stress symptoms in the child characterize the investigated population cared for in hospital — and to a lesser degree the investigated population cared for at home — compared with the control material.

Neither is there any reason to doubt that this picture applies to children for whom head injuries are reported on questioning.

The extent to which it applies to children who have actually had such acute head injuries is not immediately evident. In the discussion of methods in the epidemiologic section of the investigation, the question of what the investigated populations actually represent was thoroughly discussed. Apparently most of the acute head injuries reported to be of such a degree of severity as to be associated with unconsciousness were included in the investigated populations Although there were few cases of head injuries of lesser degrees of severity in the investigated population cared for in hospital, there is reason to suspect that a considerable number of children in the investigated population cared for at home had had much slighter acute head injuries and that the primary cerebral symptoms were exaggerated by the parents. This might seriously affect the general picture sketched above if the parents of these erroneously included children or the children themselves and their environments had shown some dis

Table 21 Percentage frequency in different sex and age groups of those variables that differentiate the investigated groups from the controls.

	Born			IH		Born			IO		Born			K	
	After 1956	1954—1956	Before 1954	Boys	Girls	After 1956	1954—1956	Before 1954	Boys	Girls	After 1956	1954—1956	Before 1954	Boys	Girls
Mother a minor at delivery	4	14	14	14	10	9	8	9	8	10	3	7	2	2	8
Mother 35 or older at delivery	8	20	20	16	19	2	0	5	4	6	17	30	5	14	18
Incomplete home in child's life	13	12	20	16	15	4	23	7	10	9	7	4	10	6	8
Mother worked early in child's life	46	50	31	45	38	32	37	33	33	36	29	28	25	28	25
Mother income 5,000 — Sw cr or more	64	62	57	55	68	48	41	39	34	46	31	40	46	36	4
Family known to social welfare board	21	9	12	15	10	9	8	14	11	11	7	4	5	5	5
Emotionally disturbed home (on home visit)	4	6		5	3	4	11	12	9	9	0	0	0	0	0
Father mentally ill (*interview*)	14	12	23	25	6	4	7	5	6	7	1	9	6	6	6
Mother mentally ill (interview)	4	9	12	10	8	18	20	18	21	15	11	12	5	9	7
Mother disturbed (both occasions)	13	12	7	13	8	16	19	19	20	15	14	4	0	4	8
Mother disturbed (*one or more occasions*)	44	33	42	39	47	33	39	45	45	34	25	17	17	21	18
Child walked early	13	16	27	23	15	19	23	27	22	26	11	12	15	13	13
Primary enuresis, school age	4	9	7	12	0	4	9	8	8	6	0	0	3	2	0
Secondary enuresis	8	3	7	9	5	4	9	3	7	2	0	0	0	0	0
Truancy	8	3	10	9	5	0	3	5	2	5	0	0	3	0	3
Repeated pilfering	4	3	20	17	0		6	12	12	2	0	0	3	2	0
Frequent headache	20	27	39	29	33	8	23	33	19	29	0	12	13	10	8
Hospitalized for accident (other)	16	20	12	20	9	9	8	11	6	9	0	0	7	2	5
Repeated seizures	4	9	7	5	10	15	17	13	12	18	4	0	5	5	0
Child psychiatric contact	4	23	21	20	14	2	3	20	11	10	3	0	9	8	0
Child disturbed (both occasions)	10	11	13	18	3	12	12	7	9	11	5	5	5	5	3
Child disturbed (one or more occasions)	42	1	30	39	30	30	19	18	24	25	18	15	12	18	15

For explanation of the symbols, see table 13

tinguishing characteristics with respect to the variables in the investigation. In this connection it is worth noting that more severe states of psychic insufficiency were strikingly common in the mothers of the investigated population cared for at home compared not only with the control material but also with the investigated population cared for in hospital (IH = 11 %, IO = 19 %, K = 6 %). Should this excess frequency in the investigated population cared for at home apply more to erroneously included children than to children who had actually had acute head injuries associated with unconsciousness and cared for at home, this would clearly affect the general picture constructed from the results of the investigation. Psychic insufficiency in the mother was correlated to the following other variables: Mother's declared income 5000:- or more, 'Emotionally disturbed home', Mother disturbed on one occasion, 'Truancy', 'Repeated seizures' and Child disturbed on one occasion. Its correlation to the variable 'Emotionally disturbed home' is expressed by the correlation coefficient PHI being as high as 0.51 and this variable would perhaps no longer differentiate the head injury material from the control material. The other correlations are low and on the whole the above would hardly affect the results in any way other than that the frequency of psychic insufficiency of the mother on home visit and at the hospital, would become more comparable for the two investigated populations and perhaps would not significantly differentiate the material cared for at home from the controls.

It can be pointed out that the variable Repeated seizures shows co-variation only with Mother disturbed on both occasions and Mother mentally ill' and not with other variables. If one chooses to regard the marked excess frequency of repeated seizures reported for the investigated population cared for at home (IH = 7 %, IO = 15 % and K = 3 %) as more representative of erroneously included children than of children with actual head injuries, this would tend to change the general picture in the way described above. However the correlations are low and this would not mean any noticeable change. It is not possible to say whether the general picture drawn from the results of the investigation should be revised in any way. It is possible that constitutional factors predisposing to psychic insufficiency and/or repeated seizures of more or less epileptic nature could be important for the occurrence of acute head injury as well as for the absence of hospital care for such injury. However the basis for such a claim is very shaky and the author himself interprets the excess frequencies of more severe psychic insufficiency in the mother and of repeated seizures in the child as reflecting the characteristics of erroneously included children, or possibly as the irrelevant results of chance.

In any case, it is most correct to emphasize the stressful circumstances in the child's environment and the stress symptoms in the child when enumerating the factors that distinguish children who have had acute head injuries from those who have not.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1)														13						
	2)	11		27		21	16		18				20	13				21		
		3)	35			12												11		
			4)					13												
				5)	22				12				33	30				34	13	13
					6)			51	38						19			14	14	19
						7)			15				16	17					19	12
							8)		21		12	17	23				18			14
								9)	57				16				11			13
									10)				18					14		22
										11)	14									
											12)							19		
												13)		12						
													14)	25	16			26		13
														15)				23		12
															16)			14		
																17)				
																	18)			
																		19)	16	14
																			20)	33

1 Mother a minor at delivery
2 Incomplete home in ch ld's life
3 Mother worked early in child's life
4 Mother s income 5 000 — Sw cr or more
5 Known to social welfare board
6. Emotionally disturbed home (on visit)
7 Father mentally ill (interview)
8 Mother mentally ill (interview)
9 Mother disturbed (both occasions)
10 Mother disturbed (one occasion)
11 Child walked early
12. Primary enuresis, school age
13 Secondary enuresis
14 Truancy
15 Pilferi g
16. Headache
17 Hospitalized for accident (other)
18. Seizures
19 Child psychiatric contact
20 Child disturbed (both occasions)
21 Child disturbed (one occasion)

T bl 22. Positive correlations between the variables whose frequencies differentiate the investigated popula tion cared for in hosp tal and/or that cared for at home from the control material by being significantly (at 0 1 level) higher n the investigated population. The significant (at 0 1 level) positive correlation between these variables is indicated by the corresponding PHI-coeffici ent (a product moment correlation coefficient)

acute head injury was denied by questionnaire in the epidemiologic section of the investigation.

The general plan of the investigation is presented, followed by a detailed description and discussion of the individual variables drawn from the home visit, the physical and neurological examination, the interview with the parent the psychological investigation, the interview with the teacher and review of the school grades, the psychiatric records for the child and the parents, the records of care for reported somatic illnesses in the child, the school dental records, the information about the family in the archives of the social welfare board (or the corresponding public agency in the community) and, finally the parents declared incomes. The methods used are discussed, and the controlled methodology including the use of simple blind technique and the observation of a staggered sequence, is shown to have functioned satisfactorily

The results are described and discussed. The variables that significantly (at the 0 1 level) differentiate either or both of the head injury materials from the control material have, in general, plausible frequencies in the control material and mainly show the sort of internal co-variation that would be expected on the basis of general clinical experience.

The results gi e a picture that is clear and consistent and the questions posed in the investigation are answered as follows

Is there any difference between the children reported to have previously been cared for in hospital for acute head injury associated with unconsciousness and/or children reported to have been cared for at home for such injury and children for whom no previous acute head injury was reported

A) with respect to unfavorable social circumstances and psychic insufficiency of the parents?

The answer is clearly 'yes' for both IH and IO Such circumstances as the mother having been a minor at the time of delivery the home having been incomplete during the child's life, the family being known to the social welfare board etc. proved to be significantly more frequent in IH than in K, IO was in an intermediate position, significantly different from K with respect to some variables but not with respect to others. Psychic insufficiency of the parents was significantly more frequent in IH (father and mother) and IO (mother) than in K, according to anamnesis and evaluation of psychic status.

B) with respect to behavioral disorders and symptoms of psychic insufficiency in the child?

The answer is clearly yes since such symptoms as primary and secondary enuresis, truancy pilfering and headache were significantly more frequent in IH than in K, with IO in an intermediate position, often but not always significantly different from K. The same is true for previous child psychiatric contact and for the presence of psychic insufficiency in the child according to the author's evaluation.

C) with respect to clinical symptoms of brain injury in the child?

The answer is clearly no since neurological and psychological investigation

Summary of the child psychiatric section of the investigation

The materials in the child psychiatric *section of the investigation are reviewed* What the head injury materials represent is thoroughly discussed in the epidemiologic section of the investigation The investigated population cared for in hospital may be satisfactorily representative of acute head injuries associated with unconsciousness that actually occurred since these reports could usually be confirmed by the hospital records and since the omissions were estimated at only 5—10 % (as judged from the number of such head injuries found by reviewing the archives of the Department of Surgery of Umeå Hospital but not reported by questionnaire) This material is clearly representative of acute head injuries associated with unconsciousness reported in practical clinical work. The investigated population cared for at home is also representative of reported acute head injuries associated with unconsciousness, but may not satisfactorily represent such head injuries that actually occurred and were cared for outside the hospital Judging from the frequency of acute head injuries associated with unconsciousness later reported for the control material (= 0) the omissions ought not to be numerous but the corresponding frequency of head injuries with other primary cerebral symptoms (1 %) suggests that the omissions may have amounted to about 10 % Moreover many cases of acute head injury associated with unconsciousness are surely never known to the parents and may have been forgotten even by the children Last, but not least, the material cared for at home would seem to have included a considerable number of cases of much slighter head injury than intended

The agreement between the information obtained by questionnaire and by telephone interview regarding the presence or absence of unconsciousness in association with the head injury is PHI 0 67 for the population cared for at home compared with 0.72 for that cared for in hospital

The investigated population cared for in hospital can be characterized as a slight head injury material, and the investigated *population cared for at home* as a very slight head injury material

The control material was selected by the process of independent random selection so that the three materials can be directly compared without corrections for age or sex so that significance at the 0 1 level corresponds to a percentage difference in frequency of the order of magnitude of 10 %, in the range of 10—20 % and so that the material represents children for whom

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ELECTROENCEPHALOGRAPHIC SECTION

S BLOM and V RUNE

and child psychiatric evaluation revealed no significant differences between the materials with respect to signs of past hemispheric damage performance on the block test, discrepancies between the results of verbal and spatial testing, or fluctuating alertness, difficulties in concentration motor unrest and perseverations. Furthermore, there were definite findings of this kind in only a few cases in the entire material.

Both non-specific and paroxysmal EEG changes in children are often interpreted as indicating that the child has at one time suffered brain damage of, for example, infectious, traumatic, pre peri- or postnatal type.

Dalison, Heller and Hellström 1965 (26) and others have maintained that this interpretation is questionable. In an EEG study of selected healthy children, Petersén and co-workers 1968 (85) found paroxysmal EEG abnormalities in 99 of 757 children investigated. In a follow-up study on 28 pairs of twins of which four pairs were under 14 years of age and in which one but not the other twin had previously suffered acute head injury with primary cerebral symptoms, Sulg and Dencker 1968 (118) found a high degree of correlation between the EEG findings in the injured and the uninjured twin, regardless of whether the EEG was normal or pathological.

That the EEG often shows clear and sometimes pronounced abnormalities during the acute phase of a head injury has been shown by Melin 1949 (77) Richter 1956 (93) Silverman 1962 (107) and Kubala and Kellaway 1967 (66) among others. Richter pointed out, as did Weinmann 1966 (122) that these changes are often relatively more pronounced in children than in adults. It is well known that EEG changes in the acute phase are more pronounced after severe head injuries associated with prolonged unconsciousness or intracranial complications than they are after slighter head injuries.

In longitudinal studies of patients hospitalized for acute head injury systematic EEG investigations have rarely been included, and the results are often hard to evaluate since the pretraumatic EEG status has not been known, no control material has been used, and the methodology has not been controlled, for example by the use of blind technique. However Nylander and Koerner 1952 (81) Rickham 1961 (94) Hjern and Nylander 1962 (54) Hendrick and co-workers 1964 (52) Weinmann 1966 (122) and Kubala and Kellaway 1967 (66) among others, have shown that in general the acute EEG changes following slight and moderately severe acute head injuries seem to be quickly reversible, with normal EEG findings again present after periods of a few weeks to a year. In the light of this, it would seem justified to maintain that a diagnosis of brain damage cannot be based on a pathological EEG alone, and that in evaluating a pathological EEG finding in a child who has previously had an acute head injury one must consider the possibility that the

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Table 23 Children Investigated with EEG.

	Boys	Girls	Total
EEG-H	9 (16)	13 (16)	22 (32)
EEG-O	14 (25)	17 (22)	31 (47)
EEG-K	6 (12)	8 (14)	14 (26)

Acute head injury associated with unconsciousness, cared for in hospital = EEG-H.
Acute head injury associated with unconsciousness, cared for at home = EEG-O
Unselected controls, taken from the primary school population for which prior acute head injury is denied = EEG-K.
The numbers of children originally selected for EEG investigation are given in parentheses.

representing only 2 % of the primary school children in Umeå in the above age group for whom acute head injury was not reported. It is so small even in absolute numbers that it is questionable whether it is representative.

Table 23 also shows the number of omissions. Only 64 % of the material could be investigated. Unfortunately the omissions in the control material were especially numerous (46 %) The authors considered drawing a control material from the archives of the Neurophysiological Laboratory in Umeå, but refrained from doing so since this would have been a digression from the principles of the investigation, and in addition would have had to be done piece meal at the end of the investigation.

The reported traumatological data for the parts of the head injury material cared for in hospital and at home respectively are shown in Tables 24 25 26 and 27 and the traumatological bias that characterizes the material actually investigated in relation to the material selected can also be read from these tables.

For a discussion of the reality behind the reported durations of unconsciousness associated with acute head injury the reader is referred to the discussion of methods in the epidemiologic section of the investigation. Here it will merely be emphasized that the injuries in the head injury materials should be regard ed as somewhat less severe than Table 27 would indicate.

METHODS

64 of the patients were investigated using a 16-channel Elema EEG-Mingograph, and three were investigated using an 8-channel Grass electroencephalograph.

21 surface electrodes were placed according to the 10—20 system. Both bipolar and monopolar (average reference) connections were used. The amplification was 10 microV/mm throughout, the paper speed was 30 mm/sec, and the time constant 0.3 seconds.

The recording included 15 minutes of recording at rest divided into five programs, three minutes of hyperventilation followed by three minutes of recording at rest, and finally stimulation with intermittent light (Elema stroboscope, frequencies 5—25/sec, stimulation time 3—4 min.)

The patients were awake during the

child has brain damage of other origin or has epilepsy

In the present study it has been possible to 1) do a follow up study not only of children who had been cared for in hospital for an acute head injury but also of children who were cared for at home for such an injury — a group not previously investigated with EEG 2) compare the findings in a head injury material with the findings in a control material especially selected for the purpose — which has not been done previously in follow up studies of acute head injury in children 3) perform EEG recording under similar circumstances in the different cases and evaluate the tracings without knowing whether the child had had an acute head injury or was suspected to have brain damage associated with such injury or due to another cause, or whether the child had had convulsions.

The main question posed in the investigation was the following

Are children who have previously been cared for in hospital for acute head injury associated with unconsciousness and/or children who have previously been cared for at home for such an injury more likely to have EEG changes than children who have not had an acute head injury?

MATERIAL

In answer to a questionnaire sent to the guardians of all the primary school children in Umeå whose home address, according to the pupil register was in Umeå proper (5 105 children) the parents of 776 children reported that the child had at some time suffered such a severe head trauma that they had been seriously worried about it. Information as to the degree of severity of the primary cerebral symptoms associated with the reported head injury was gathered one year after the questionnaire survey (spring, 1968) by one of the authors (V R.) in a telephone interview with the parents The children reported to have been unconscious in association with the head injury (271 children) were selected for child psychiatric study along with 100 control children (chosen by independent random selection from among the 4 329 children for whom no previous acute head injury was reported on the questionnaire in 1967)

The aim was to conduct an EEG investigation of the 271 children with previous acute head injury and the 100 control children, all of whom were the subjects of a broad child psychiatric and epidemiologic investigation. However various practical considerations made it necessary to greatly reduce the size of the material

For the EEG investigation were selected from this material the children who were born in 1955 1956 and 1957 and who at the start of the investigation in the fall of 1968 made up a relatively homogeneous material aged 10—13 years. (See Table 1)

The material came to have the size and composition shown in Table 23 The age distribution is even. It should be emphasized that the head injury groups are populations, and that the findings that characterize them are as well-established as the methodology would permit On the other hand, the control material is a very small sample

Table 23. Children investigated with EEG.

	Boys	Girls	Total
EEG H	9 (16)	13 (16)	22 (32)
EEG-O	14 (25)	17 (22)	31 (47)
EEG K	6 (12)	8 (14)	14 (26)

Acute head injury associated with unconsciousness, cared for in hospital = EEG-H
Acute head injury associated with unconsciousness, cared for at home = EEG-O
Unselected controls, taken from the primary school population for which prior acute head injury is denied = EEG-K.
The numbers of children originally selected for EEG investigation are given in parentheses.

representing only 2 % of the primary school children in Umeå in the above age group for whom acute head injury was not reported. It is so small even in absolute numbers that it is questionable whether it is representative.

Table 23 also shows the number of omissions. Only 64 % of the material could be investigated. Unfortunately the omissions in the control material were especially numerous (46 %). The authors considered drawing a control material from the archives of the Neurophysiological Laboratory in Umeå, but refrained from doing so since this would have been a digression from the principles of the investigation and in addition would have had to be done piecemeal at the end of the investigation.

The reported traumatological data for the parts of the head injury material cared for in hospital and at home respectively are shown in Tables 24 25 26 and 27 and the traumatological bias that characterizes the material actually investigated in relation to the material selected can also be read from these tables.

For a discussion of the reality behind the reported durations of unconsciousness associated with acute head injury the reader is referred to the discussion of methods in the epidemiologic section of the investigation. Here it will merely be emphasized that the injuries in the head injury materials should be regarded as somewhat less severe than Table 27 would indicate.

METHODS

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The patients were awake during the

Table 24 Year in which the head injury occurred.

	1958	1959	1960	1961	1962	1963	1964	1965	1966
EEG-H	—(—)	— (1)	3 (5)	5 (6)	2 (4)	1 (2)	3 (4)	3 (5)	5 (5)
EEG-O	4 (6)	2 (4)	4 (7)	7 (9)	— (3)	1 (1)	5 (6)	2 (4)	6 (7)
Total	4 (6)	2 (5)	7(12)	12(15)	2 (7)	2 (3)	8(10)	5 (9)	11(12)

For explanation of the symbols, see table 23

Table 25 Ages of children in the EEG investigation at the time of head injury

	0 years	1 years	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years
EEG-H	— (1)	—(—)	2 (3)	1 (2)	2 (4)	3 (5)	3 (4)	2 (3)	3 (3)	4 (5)	1 (1)	1 (1)
EEG-O	1 (2)	4 (5)	3 (5)	5 (7)	3 (3)	2 (3)	1 (3)	3 (5)	2 (4)	6 (7)	1 (2)	— (1)
Total	1 (3)	4 (5)	5 (8)	6 (9)	5 (7)	5 (8)	4 (7)	5 (8)	5 (7)	10(12)	2 (3)	1 (2)

For explanation of the symbols, see table 23

Table 26. The type of accident producing the head injury

	FALL FROM				TRAFFIC ACCIDENT	OTHER
	at least 2 m	*½—2 m*	*0—½ m*	*vehicle*		
EEG H	2 (4)	6 (8)	3 (5)	5 (7)	5 (6)	1 (2)
EEG-O	2 (2)	11 (17)	6 (12)	8 (12)	2 (2)	2 (2)
Total	4 (6)	17 (25)	9 (17)	13 (19)	7 (8)	3 (4)

For explanation of the symbols, see table 23

Table 27 The reported duration of unconsciousness associated with the head injury

	At least 30 min	5—30 min	Less than 5 min
EEG-H	4 (7)	4 (9)	14 (16)
EEG-O	— (—)	3 (6)	28 (41)
Total	4 (7)	7 (15)	42 (57)

For explanation of the symbols, see table 23

entire recording. Complementary recordings during sleep would of course have been desirable — Rodin 1967 (97) and Petersén et al. 1968 (85) — since certain EEG abnormalities do not appear except during sleep especially in children. However since it was not possible to carry out sleep recordings in a consistent manner we chose to restrict the investigation to recordings in the waking state.

The slip referring the subject to the laboratory gave the subject's name, date of birth, information as to any medication he might be taking, and the fact that he was taking part in the investigation. The author who evaluated the EEG tracings (S. B.) know nothing more about the subject, nor did he know the relative size of the material or the general degrees of severity in the head injury materials. The EEG tracings were evaluated both as the investigation progressed during the period October 1968 to March, 1969 and during a more concentrated 15-day period of evaluation 5—10 months later. At each evaluation it was noted whether the EEG was normal, and, if not, the type of abnormality present, its extent and prominence. This description and a summary of the evaluation of the tracing were recorded on a special form using the terminology recommended by the Terminology Committee of the International Federation for Electroencephalography and Clinical Neurophysiology 1966 (87).

Normal and borderline EEG's were combined in a normal group. Abnormal EEG's were classified as slightly moderately or severely abnormal. (However no severely abnormal EEG's were found.)

In 75 % of the cases there was complete agreement between the two classifications of the EEG. In no case was there a discrepancy of more than one grade.

No importance was attributed to the slight asymmetries in the amplitude of alpha activity that are often seen in the age group in question. A slow rhythm component increased for this age group was regarded as a nonspecific abnormality and was described as limited or general, continual or episodic, present at rest or occurring only on activation. Spikes, sharp waves and wave-and-spike rhythms were designated paroxysmal activity and were described as to localization and whether they were present in the recordings during rest or only on activation.

RESULTS

The EEG findings for the group cared for in hospital are given in Table 28. Of the six nonspecific abnormalities,

Table 28. EEG findings in the part of investigated population cared for in hospital selected for EEG investigation

Normal EEG	Slight, nonspecific abnormalities	Slight, paroxysmal abnormalities	Moderate, nonspecific abnormalities	Moderate, paroxysmal abnormalities
13	4	2	2	1

Table 29 EEG findings in the part of investigated population cared for at home selected for EEG investigation.

Normal EEG	Slight, nonspecific abnormalities	Slight, paroxysmal abnormalities	Moderate, non-specific abnormalities	Moderate, paroxysmal abnormalities
20	5	4	1	1

Table 30 EEG findings in the part of the control material selected for EEG investigation.

Normal EEG	Slight, nonspecific abnormalities	Slight, paroxysmal abnormalities	Moderate, non specific abnormalities	Moderate, paroxysmal abnormalities
6	5	3	—	—

four were diffuse and without lateral preponderance: two were localized but lacked a distinct focus. All of the paroxysmal abnormalities occurred in connection with activation in two cases on photostimulation and in one case on both photostimulation and hyperventilation

The EEG findings in the group cared for at home are given in Table 29 Four of the six nonspecific abnormalities were symmetrical with diffuse spreading and one was localized but not completely demarcated In five of the ten cases of paroxysmal abnormality this occurred only in connection with hyperventilation and photostimulation and in four of the cases was regarded as slight In the other five cases the abnormality was present even in the recording at rest In two children there were generalized bilateral synchronous wave and spike rhythms in the remaining three children there was focal centro-temporal abnormality (two children) and fronto-temporal abnormality (one child)

The EEG findings for the control material are given in Table 30 Two of the five nonspecific abnormalities were diffuse and showed no asymmetry but three were localized to the left fronto-temporal region without being focally demarcated In two cases the paroxysmal abnormality consisted of sporadically occurring, sharp centro-temporal waves in the third case a slight paroxysmal response was recorded on photostimulation

DISCUSSION

The small size of the control material and the number of omissions mean that there can be no reliable statistical conclusions about the EEG findings for the groups This is unfortunate, but unavoidable

The authors wish to emphasize that the evaluation of EEG's is a subjective method with respect to findings other than distinct definable patterns such as alpha frequency and alpha amplitude, spikes, sharp waves and wave-and

spike rhythms. The nonspecific abnormalities found in the present investigation (in the older EEG literature called dysrhythmias) in some cases might have been regarded as normal variations by another investigator

There were no differences between the head injury groups and the control group with respect to the presence of nonspecific abnormalities. Paroxysmal abnormalities seemed to be more frequent in the group cared for at home than in the other groups, but the difference from the control group is not significant.

However in the child psychiatric section of the investigation it was found that at least three prior episodes of grand mal type seizures atypical seizures, febrile convulsions, affect convulsions or fainting was reported significantly more often for the children of school age cared for at home for acute head injury associated with unconsciousness than for the children in the control material. The corresponding investigated group cared for in hospital was intermediate in this respect.

In two of the six cases in the head injury group cared for at home that were judged to have moderate paroxysmal abnormalities, febrile convulsions were reported to have occurred in the toddler and preschool ages In a third case, generalized tonic convulsions were reported to have occurred at the same ages

It is thus possible that paroxysmal EEG activity is more often present in children reported by their parents to have suffered an acute head injury than in other children.

This is most easily explained if one supposes that the parents misinterpreted unconsciousness as due to cerebral concussion, when it instead had resulted from a seizure. There is reason to be very cautious in interpreting paroxysmal abnormalities in children reported to have had acute head injury

In 9 of the 16 cases in which paroxysmal activity was found this was present only on activation. Such changes were found in 5 % of a material of selected healthy children described by Petersén and co-workers 1968 (85) The abnormality should thus be interpreted with caution. The same is presumably true of the sharp waves in the centro-temporal regions that are sometimes called Rolandic spikes, (Blom and Brorson 1966) (15)

SUMMARY

1 No differences were found with respect to the presence of normal and/or pathological EEG patterns between a head injury material cared for in hospital, a head injury material cared for at home and an unselected control material.

2. The limited size of the materials does not permit a reliable detailed analysis of possible differences between the groups with respect to the types of abnormalities that were found

3 From the clinical point of view the EEG should be evaluated with great caution after head injury in children (following the acute phase) especially if it is not possible to compare the findings with the EEG pattern before head injury

Table 29 EEG findings in the part of investigated population cared for at home selected for EEG investigation.

Normal EEG	Slight, nonspecific abnormalities	Slight, paroxysmal abnormalities	Moderate, non specific abnor malities	Moderate, paroxysmal abnor malities
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The small size of the control material and the number of omissions mean that there can be no reliable statistical conclusions about the EEG findings for the groups. This is unfortunate, but unavoidable

The authors wish to emphasize that the evaluation of EEG s is a subjective method with respect to findings other than distinct definable patterns such as alpha frequency and alpha amplitude spikes sharp waves, and wave-and

SUMMARY AND CONCLUSIONS

On surveying the relevant literature, the author found knowledge about the epidemiology of acute head injury in children to be incomplete, and the question whether children who have suffered an acute head injury are more likely then other children to exhibit signs of behavioral disturbances and psychic insufficiency to be still unanswered, although it has been of interest for generations.

The author chose to conduct a retrospective investigation of primary school children, first by means of a questionnaire mailed to the parents, secondly by telephone interview with the parents who reported that the child had suffered such a severe blow to the head that we were seriously worried about it and then by a broad child psychiatric study of the children who were reported to have been unconscious in association with the acute head injury (101 cared for in hospital, 170 cared for at home) and of control children (100) chosen by independent random selection from among children for whom head injury was denied on the questionnaire. All the head injury materials can be regarded as representative of acute head injuries, of different degrees of severity with respect to primary cerebral symptoms, reported in clinical practice. The latter part of the investigation was carried out without the investigators knowing to which material a child belonged. When a part of the investigation extended over a longer period of time, a staggered sequence procedure was used.

Samples of the two head injury materials in which unconsciousness was reported to have been present — cared for at home and in hospital respectively — and of the control material, were investigated by EEG

Acute head injuries associated with primary cerebral symptoms of some degree of severity were reported for 9 % of the primary school population (33 % had been cared for in hospital) The risk of incurring such a head injury during the course of a year was estimated at 1 / for schoolboys and 1/2 % for schoolgirls, with a lesser risk and a negligible sex difference during the pre school years.

The children cared for in hospital had generally had more severe primary cerebral symptoms than those cared for at home, and in the former group the injury was more often due to a traffic accident Toddlers and infants were relatively less often cared for in hospital for an acute head injury associated with cerebral symptoms.

Compared with control children, the children reported to have had acute

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The children cared for in hospital had generally had more severe primary cerebral symptoms than those cared for at home, and in the former group the injury was more often due to a traffic accident. Toddlers and infants were relatively less often cared for in hospital for an acute head injury associated with cerebral symptoms.

Compared with control children, the children reported to have had acute

head injury associated with unconsciousness were characterized by such psychic symptoms as primary enuresis, secondary enuresis truancy, pilfering, and headache they had more often had contact with a child psychiatric clinic and were more often judged by the author to be psychically insufficient. The children who had been cared for at home for such head injuries were in an intermediate position between the children cared for in hospital and the control children

Neurological, child psychiatric, psychological and electroencephalographic investigation showed no differences between the materials with respect to the frequencies of various signs of brain damage. Brain damage was directly suspected in only a few cases.

On the other hand the milieu of the children cared for in hospital and to a lesser extent of those cared for at home was more often characterized by an incomplete home, need for social welfare assistance and other unfavorable circumstances, and, in addition by psychic insufficiency of the parents.

It thus appears that when a material of children who are reported to have had acute head injuries is investigated with a controlled methodology and compared with an adequately selected control material, the results are consistent with the prognosis of acute head injury outlined in recent literature: acute head injuries without clear evidence of serious brain damage in the acute phase give rise to psychic symptoms and problems of adjustment only when the child s situation is complicated by a defective environment and/or previous behavioral disorders, or when the child already has symptoms of psychic insufficiency

This, of course, does not mean that slight and moderately severe acute head injuries in children cannot cause brain damage, but it does provide an important guide for practical child psychiatric work with these children. It is the author s opinion that such work should be planned and conducted as if there were no history of head injury and that extensive, costly and time-consuming investigations aimed at detecting brain damage should in general be reserved for the cases in which the acute clinical course of the head injury gives clear reason to suspect brain damage

ACKNOWLEDGEMENTS

So many have contributed to the completion of this investigation that their names would form a long list indeed. The subjects and their parents, without whose cooperation the research could not have been conducted, must remain anonymous. I wish to take this opportunity to thank all who have helped to make this study possible.

The epidemiologic and child psychiatric sections of the investigation were carried out at the Department of Child Psychiatry, Umeå University. The head of the Department, Ingvar Nylander, not only stimulated me to undertake this research project, but has followed the work with great interest, contributing sound advice and inspiring ideas. He has gone out of his way to put me in contact with the opinions and advice of experts in relevant neighboring fields of medicine and other sciences and has facilitated my work in every way. I am deeply grateful to Professor Nylander for all his help.

The electroencephalographic section of the investigation was carried out at the Department of Neurophysiology, Umeå University. It has been a pleasant and valuable experience to cooperate with Sigfrid Blom, the head of the Department, who has also followed the work as a whole with great interest and has offered constructive criticism for which I am most grateful.

For invaluable suggestions, advice and criticism in regard to the design of the investigation, my thanks are due to Carl Erik Särndal, head of the Statistics Department of the University of Umeå, and to many members of his staff, especially Lennart Gustavsson and Jan Granåsen who also performed the statistical operations.

I have had the opportunity to discuss problems of method and analysis with Ragnar Berfenstam and members of his staff at a seminar at the Department of Social Medicine, Uppsala University. I wish to express my warm thanks for this and for the valuable criticism and advice given me on that occasion.

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Britta Östilä helped in the work with the questionnaire Eva Runström carried out the psychological part of the investigation Vera Andersson interviewed the teachers, Edit Lindgren collected most of the hospital records To these, and all other collaborators I wish to express my warm thanks for their good work and for very pleasant cooperation

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TABLE OF CONTENTS

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 208 1970

THE DEVELOPMENT OF THE ELECTROENCEPHALOGRAM IN NORMAL CHILDREN AND ADOLESCENTS FROM THE AGE OF 1 THROUGH 21 YEARS

BY ORVAR EEG OLOFSSON

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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CONTENTS

This survey is based on the following papers, which will be referred to in the text by the Roman numerals.

I PETERSÉN I and EEG-OLOFSSON O The development of the electroencephalogram in normal children from the age of 1 through 15 years. Non paroxysmal activity
Neuropädiatrie in press.

II EEG-OLOFSSON O., PETERSÉN I and SELLDÉN U The development of the electroencephalogram in normal children from the age of 1 through 15 years. Paroxysmal activity
Neuropädiatrie, in press.

III EEG-OLOFSSON O The development of the electroencephalogram in normal children from the age of 1 through 15 years. 14 and 6 Hz positive spike phenomenon
Neuropädiatrie, in press.

IV EEG-OLOFSSON O The development of the electroencephalogram in normal adolescents from the age of 16 through 21 years.
Neuropädiatrie, in press.

In this survey the following abbreviations will be used
F = female M = male
Fr = frontal T = temporal C = central P = parietal O = occipital
R = right L = left
SIL = slight increase of low frequency activity
MIL = moderate increase of low frequency activity
SPR = rhythmic 2.5—4.5 Hz activity n posterior derivations
HV = hyperventilation
I.PH.S. = intermittent photic stimulation
14-6-PS = 14 and 6 Hz positi e spike phenomen
S.D = standard deviation
Hz = Hertz (cycle per second)
μV = microvolt

"It is then around the cerebrum,
its physiological and psychological
attributes, that the main interest
of biology must ultimately turn."
(Sherrington)

INTRODUCTION

The statement by Berger (3) that age is of significant importance for the individual's electroencephalogram (EEG) resulted in a series of investigations mainly concerning the changes of alpha frequency in relation to age (4, 5, 46, 47, 48, 67, 68, 69, 70). Subsequently these publications, basic for electroencephalography, were followed by several handbooks and atlases concerning the EEG in man (14, 18, 24, 27, 28, 29, 30, 45, 56).

Extensive investigations of representative normal series provide knowledge that is indispensable if one is to assess adequately the diagnostic and prognostic significance of the EEG in various diseases and lesions affecting the brain. For studies on the development of EEG in growing individuals, it is not easy to obtain representative series of normal subjects since there is great inter- and intra-group variability. Thus it is necessary to sample an adequate number of subjects in each age group.

There is only one work, which on the whole corresponds to the aforementioned demands, that of Gibbs and Gibbs (see 29). Unfortunately this work as well as other surveys concerning the EEG in so-called normal children and young persons demonstrates certain deficiencies such as the lack of or poorly described criteria of normality, sparse information on the composition of the material and somatic examination, as well as few results from at rest registration and activations such as hyperventilation, intermittent photic stimulation, and sleep all carried out on the same subjects. Some reports as a rule deal more extensively with only certain selected EEG parameters. Other investigations have been carried out on too few subjects to allow valid statistical conclusions to be established, and rarely has an analysis been made of the influence of sex. As regards EEG studies on adolescents aged 16 through 21 years these have been reported either together with children or as a part of adult groups. Besides, a great number of the reports only concern males.

INTRODUCTION

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PURPOSE OF THE PRESENT INVESTIGATION

The purpose of the present investigation is twofold

1 To describe the EEG findings which appear in resting EEG and during activations in normal children and adolescents from the age of 1 through 21 years these findings will be related to age and sex
2 To provide a model for normally existing EEG findings, which in clinical diagnostic work can be used in the evaluation of EEG in connection with different disease states.

MATERIAL

As regards the recruitment of subjects for this investigation the aim has been not to include children possessing special signs or symptoms, which ex juvantibus imply a risk for the appearance of certain EEG patterns looked upon as abnormal

The following criteria of normality were established

1 *An uneventful prenatal perinatal and neonatal period* A gestational age not less than 37 weeks and a birth weight above 2 500 g (77) A normal delivery thus excluding face forehead, breech and transverse presentations, Cæsarean section extraction by forceps, vacuum extraction, asphyxia, and cyanotic spells
2 *No disorders of consciousness* However no subject was rejected for occasional syncope due to e g vasodepressor reactions attributable to such factors as prolonged standing acute pain or fear (1)
3 *No head injury with cerebral symptoms* such as mental confusion, apathy vomitings, headache or lightheadedness (36)
4 *No history of central nervous system diseases* e g meningitis or meningo-encephalitis.
5 *No obvious somatic diseases* which secondarily may affect the central nervous system, e g disorders of the heart, arterial hypertension endocrine disorders, and neoplastic disease.
6 *No convulsions* of emotional, febrile or other nature
7 *No family history of convulsive disorders other than those secondary to acquired cerebral damage* There has been demonstrated a higher incidence of EEG changes, mainly of paroxysmal character among close relatives of individuals with epilepsy than in controls (10 11 12, 16 17 35 54)
8 *No paroxysmal headache or abdominal pain* In connection with these symptoms various divergent EEG changes, with preponderance for those of paroxysmal character have been described (7 25 37 43 44 66) As regards headache, however no importance was attached to mild transient symptoms, such as those associated with temporary over strain, with uncorrected refractive defects, or with menstruation Subjects with headache and abdominal pain of non paroxysmal nature were rejected if the symptoms were frequent or had given rise to medical examination
9 *No enuresis or encopresis after the fourth birthday* This age limit corresponds to that reported by Hallgren (34) and Bellman (2) EEG changes mainly of paroxysmal character have been described in enuresis by Campbell and Young (13) and Fermaglich (23) In children with encopresis Bellman (2) found EEG changes representing the variety of pathological findings which

can occur Transitory urinary wetting due to urinary tract infection did not lead to exclusion.

10 *No tics stuttering, pavor nocturnus or excessive nailbiting* The significance of these factors as neurotic traits (also including paragraph 9 above) has been thoroughly discussed by Macfarlane *et al.* (51) Valentine (74) Regnér (62, 63), and Jonsson and Kälvesten (39) Nailbiting of slight extent is so frequent among school children that it must be looked upon as an ordinary activity (9 39 74) EEG changes in relation to behavioral disorders have been reported by Stevens *et al* (72) and Christozov and Dascalov (15)

11 *No obvious mental diseases e.g* psychosis, depression or obsessive compulsive symptoms.

12 *No conduct disorders e.g* delinquency or criminality

13 *No deviation with regard to mental and physical development.* This was roughly estimated by questioning the parents about certain developmental milestones and from observation of the children. In addition school children had to attend ordinary class. With respect to intelligence quotient the limit between ordinary class and special class is about 85 according to Terman Merrill (see 62)

Recruitment

The recruitment of the children proceeded from 1965 through 1968, while the adolescents were recruited during 1968 and 1969 Children younger than one year were recruited but not included in this investigation, as a separate EEG study on normal children during their first year of life will be published from this laboratory (33).

To collect the subjects for the investigation well-baby clinics, child-care homes, nursery schools, common schools, trade schools, schools for education of nurses, physical therapists, and secretaries, as well as military and municipal institutions were notified. The final material was filtered out by 3 different procedures of selection

1.st (rough) selection

Via the aforementioned institutions notice was distributed, which briefly described the investigation and presented the conditions to be fulfilled in order to participate (Appendix A, paper I) As regards the children this notice was directed to the parents, while the older subjects were asked to contact their parents, if they lived outside the Göteborg region. Approximately 30 per cent positive responses to the notices were obtained.

2nd (control) selection

Subjects who had expressed interest were telephoned (the author) and questioned in regard to the just described normality criteria. A number of individuals were rejected as these criteria were not met; others had changed their minds or could not accept the time for examination; still others were never contacted as the requirements in certain age groups were met.

The number of subjects arriving at the laboratory for examination was 1,300.

3rd (examination) selection

Past history

When the subjects and, in regard to the children, usually one of the parents arrived at the laboratory the individual past history was more extensively penetrated (the author or occasionally another physician) according to questionnaire (Appendix B, paper I). In addition some social and family data were noted including that required to request the delivery files.

Somatic examination

After the history was taken, somatic examination was performed; this emphasized neurological status according to special schedule (Appendix C, paper I).

Handedness could be adequately judged from 3 years of age by questioning and testing according to criteria applied by Bingley (8).

In regard to the adolescent group, body-build examination, a psychological interview and an intelligence test were administered. The results of these investigations will be separately reported by Eeg Olofsson (19), and Berzler and Eeg-Olofsson (6).

Delivery files

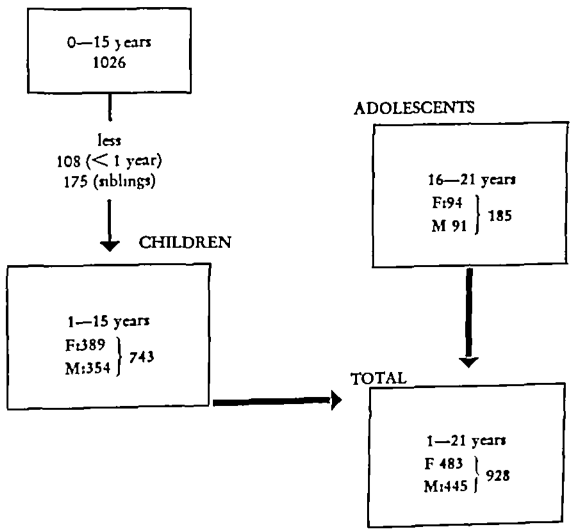
All delivery files were ordered, and all but 34 were received. Thus in 96 per cent of the subjects the delivery data could be checked retrospectively. As regards the remaining 4 per cent, these subjects were accepted on the basis of history and somatic examination without deviating findings.

Subjects rejected

At the medical penetration of the history or at the somatic examination it was found that 57 subjects did not meet the criteria of normality; the control of delivery files revealed a pathologic prenatal and perinatal course in 32 cases. Thus a total of 89 subjects were rejected.

Subjects investigated

Only subjects without mutual kinship in the ages from 1 through 21 years were investigated. They are considered in two groups, children and adolescents, as indicated below.



Description of the material

The 928 subjects comprising this material are divided according to age, sex, and number participating in resting EEG and *different* activations (Table I). A description of the material was performed according to age at puberty birth order in family and left handedness as well as marital status, and social group of the parents (Table II) Deviating signs which have been accepted are also described.

Comments

The cause of sporadic syncope was orthostatism or in most cases pain or fear As occasional syncope is regarded as a physiologic phenomenon (1 22, 53 65) these children were not rejected.

In addition it was observed that parents or siblings of 47 subjects or 5 per cent had sought medical advice for psychic complaint, usually of depressive nature. This was not considered as a criterion for rejection.

As regards puberty this is usually determined in females by the age of menarche. In males there is no such suitable index therefore the age of deepening of voice was chosen as being most convenient for an investigation like this.

In the adolescent females, the phase of the menstrual cycle, at which the EEG examination was carried out, was noted 13 per cent were in the menstrual, 35 per cent in the

Tabl I Age and sex distribution of 928 children and adolescents 1 through 21 years with recordings at rest and during different activation procedures.

Age	At rest			HV			LPHS.			Sleep		
(yrs)	F	M	F+M	F	M	F+M	F	M	F+M	F	M	F+M
1	15	19	34	—	—	—	9	13	22	13	18	31
2	23	24	47	—	—	—	21	19	40	22	23	45
3	22	21	43	6	5	11	19	16	35	21	19	40
4	26	20	46	17	15	32	23	20	43	22	19	41
5	18	22	40	17	21	38	16	19	35	18	20	38
6	19	23	42	19	23	42	14	18	32	16	18	34
7	24	24	48	24	24	48	22	21	43	22	20	42
8	35	29	64	35	29	64	27	26	53	25	24	49
9	28	19	47	28	19	47	21	17	38	20	14	34
10	28	31	59	28	31	59	23	22	45	22	20	42
11	28	16	44	28	16	44	21	13	34	19	13	32
12	33	27	60	33	27	60	21	20	41	21	17	38
13	28	31	59	28	31	59	23	24	47	22	22	44
14	35	33	68	35	33	68	32	29	61	30	26	56
15	27	15	42	27	15	42	24	12	36	22	11	33
16	15	15	30	15	15	30	15	15	30	15	15	30
17	16	16	32	16	16	32	16	16	32	15	16	31
18	15	15	30	15	15	30	15	15	30	15	15	30
19	16	15	31	16	15	31	16	15	31	16	15	31
20	17	15	32	17	15	32	17	15	32	17	15	32
21	15	15	30	15	15	30	15	15	30	15	15	30
1—21	483	445	928 (100)	419	380	799 (86)	410	380	790 (85 /)	408	375	783 (85)

(For abbreviations see page 4)

Delivery files

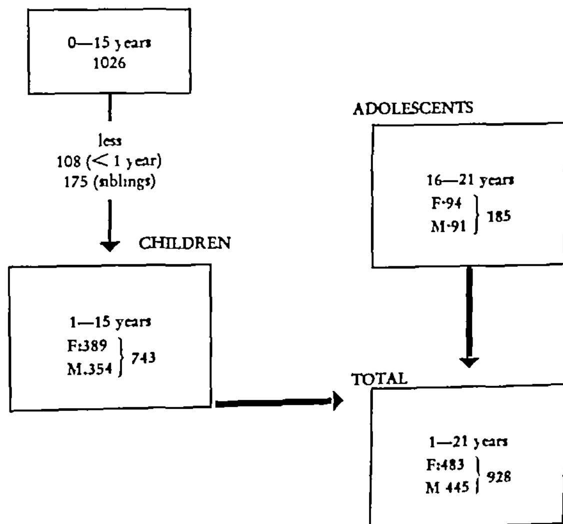
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[illegible]

The [illegible] EEG and [illegible] (Table I). [illegible] (Table II). [illegible]

Comments

[illegible]

[illegible] EEG [illegible]

Table [illegible]

[illegible]

Delivery files

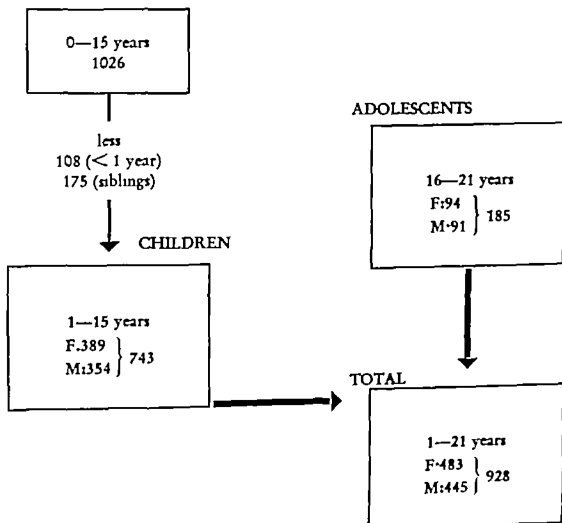
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In the adolescent females, the phase of the menstrual cycle, at which the EEG examination was carried out, was noted: 13 per cent were in the menstrual, 35 per cent in the

Table I. Age and sex distribution of 928 children and adolescents 1 through 21 years with recordings at rest and during different activation procedures.

Age (yrs.)	At rest F	At rest M	At rest F+M	*HV* F	*HV* M	*HV* F+M	*LPHS.* F	*LPHS.* M	*LPHS.* F+M	*Sleep* F	*Sleep* M	*Sleep* F+M
1	15	19	34	—	—	—	9	13	22	13	18	31
2	23	24	47	—	—	—	21	19	40	22	23	45
3	22	21	43	6	5	11	19	16	35	21	19	40
4	26	20	46	17	15	32	23	20	43	22	19	41
5	18	22	40	17	21	38	16	19	35	18	20	38
6	19	23	42	19	23	42	14	18	32	16	18	34
7	24	24	48	24	24	48	22	21	43	22	20	42
8	35	29	64	35	29	64	27	26	53	25	24	49
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12	33	27	60	33	27	60	21	20	41	21	17	38
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14	35	33	68	35	33	68	32	29	61	30	26	56
15	27	15	42	27	15	42	24	12	36	22	11	33
16	15	15	30	15	15	30	15	15	30	15	15	30
17	16	16	32	16	16	32	16	16	32	15	16	31
18	15	15	30	15	15	30	15	15	30	15	15	30
19	16	15	31	16	15	31	16	15	31	16	15	31
20	17	15	32	17	15	32	17	15	32	17	15	32
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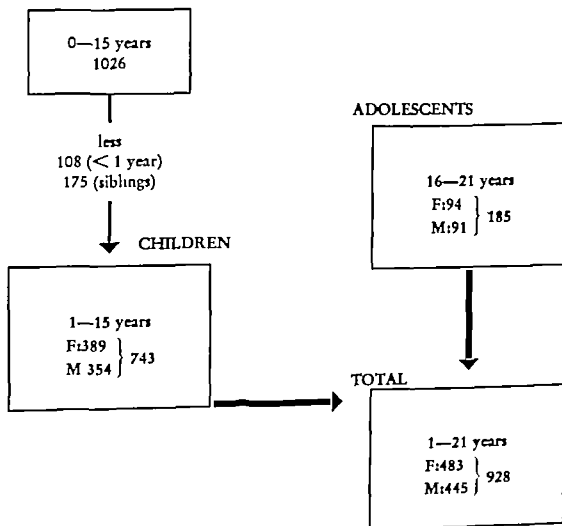
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METHODS

EEG recordings

The EEGs were taken with either Grass or Kaiser electroencephalograph. In most cases 8 channels were used for the EEG, and 2 for recording eye movements. *The 10—20 electrode system of the International Federation* (38) was used with the customary longitudinal and transverse bipolar derivations. In all recordings 1 montage with common reference lead (homolateral ear) was also used. Two ear leads designated A_1, B_1 and A_2, B_2, respectively were used. The paper speed was 3 cm/sec., the time constant 0.3 sec. and the filter 70 Hz. The procedure was as follows

Recording at rest usually occupied the initial 30 minutes, if the subject did not fall asleep at the onset of registration. Running notes have been made in the resting EEG regarding the occurrence of drowsiness of the subject. Alerting stimuli such as visual stimuli, eye opening or eye winking, or auditory stimuli, were performed several times during the recording.

Hyperventilation was attempted from the age of 3 years. It was performed for 3 minutes. The subjects were encouraged to draw as deep breaths as possible, and a respiration rate of about 20 per minute was obtained. The recording was continued until 2 min. after hyperventilation.

Intermittent photic stimulation was carried out by means of a Kaiser stroboscope (electrical energy = 0.2 joule/flash maximum intensity at 10 flashes/sec.: 1.8 megalux). The lamp distance was 15 cm. Flashes were produced in the following sequences *rising course* — 4, 6, 8, 11, 13, 20, 24 flashes/sec., each frequency lasting 40 sec.; *declining course* — 20, 18, 16, 15, 14, 13, 12, 11, 10, 8, 6, 4 flashes/sec., each lasting 20 sec.; 4 flashes/sec., and 24 flashes/sec. alternatively for 5 sec. on 10 consecutive occasions, and finally 13 flashes/sec. 6 times for 5 sec., with an interval of 15 sec. between each stimulation period.

Sleep records including a run of about 10 to 70 minutes light sleep were made. When sleep was not *yielded spontaneously* it was induced by oral or rectal administration of barbiturate (pentobarbital sodium) — 1 to 5 years 50—90 mg; 6 to 11 years 80—110 mg; 12 years and more 100—150 mg. The dosage also depended on the weight of the subject and the degree of alertness.

Analysis of the EEG recordings

A resting EEG was done in all of the children the activations, however were performed in different numbers partly depending on age (Table I see also Table II paper I). In the adolescent group resting EEG and activations were carried out in all subjects except one female of 17 who did not sleep in spite of barbiturate induction, but attained deep drowsiness.

The records were evaluated for representing waking, drowsiness, or light sleep according to the classification by Loomis *et al.* (49 50). Absence of drowsiness was a condition for the estimation of alpha, beta, and many low frequency activities as will be shown in Table III some low frequency EEG patterns appeared only in drowsiness. The different EEG patterns were described regarding frequency amplitude, location, incidence, and, if relevant, reaction to alerting stimulus.

In Table III all patterns recorded at rest as well as during HV I.P.H.S. and sleep are described. The appearance of some characteristic wave forms and patterns are illustrated.

Comments

The estimation of frequencies and amplitudes has been described in detail in paper I. The classification of the resting records in "super normal" "normal SIL, and MIL (*Figs. 1 2, 3*) was based on a visual estimation of the amount of non rhythmic low frequency activity in relation to age. This working" nomenclature has no diagnostic or *prognostic* meaning. This is important to mention, as it is difficult to establish what can be interpreted as a *normal EEG* A longitudinal study of the material investigated must be performed before a definition can be applied.

In order to increase the accuracy and obtain objective means for evaluating EEG phenomena, automatic frequency analysis on parts of the child material and the whole adolescent material proceeded simultaneously As regards the amount of non-rhythmic low

Table II Description of the material.

			Child group (1—15 yrs.)		Adolescent group (16—21 yrs.)		Total (1—21 yrs.)
Age at puberty (yrs.)	Female		13.2	(median values)	12.8 (S.D ±1.2)	(mean values)	
	Male		14.2		14.1 (S.D ±0.9)		
First child (%)			39.2		45.4		40.4
Left-handedness (%)			11.0		9.2		10.6
Parents marital status (%)							
Married			90.6		86.6		89.9
Divorced			6.5		9.1		7.0
Widow/Widower			1.5		3.8		1.9
Single			1.4		0.5		1.2
Parents social group (%)							
I		8	29	(28)	20		27
II		38	36	(22)**	43		38
III		54	35	(50)**	37		35
Deviating signs which have been accepted (%)							
Sporadic syncope	Female		2.3		22		6.2
	Male		0.8		11		2.9
Slight nailbiting			7.4		9.2		7.8
Hereditary ptosis			0.4		—		0.3

Figures for Göteborg city (from the Statistical Bureau of the City of Göteborg, based on the register of voters from 1968)

** Figures for children rejected.

proliferative and 52 per cent in the secretory phase Nineteen of these females (20 %) used contraceptive pills.

The division into 3 social groups (59) was made in accordance with the social grouping adopted in the Official Election Statistics of Goteborg (60) The groups are designated I II and III the higher figure representing the lowest group This is hitherto the most common method in Sweden and is mainly based on a grouping of vocations.

Conditions at the EEG examination

The EEG examinations could be executed at 7 a.m., 10 a.m., 12.30 p.m., or 4 p.m The children were requested for practical reasons to come for the EEG examination at 12.30 p m and 86 per cent accepted this time. For the adolescents this was an inconvenient time 37 per cent of them arrived at 12.30 p.m and 52 per cent at 4 p.m.

In case of illness on the proposed day of examination the subjects were requested to arrange for a new appointment. *Information* had been given earlier in order to avoid the influence of hypoglycemia, raised body temperature and fatigue on the EEG Mild catarrhal symptoms accompanied by a body temperature not exceeding 37 8 C did not exclude the subject.

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Comments

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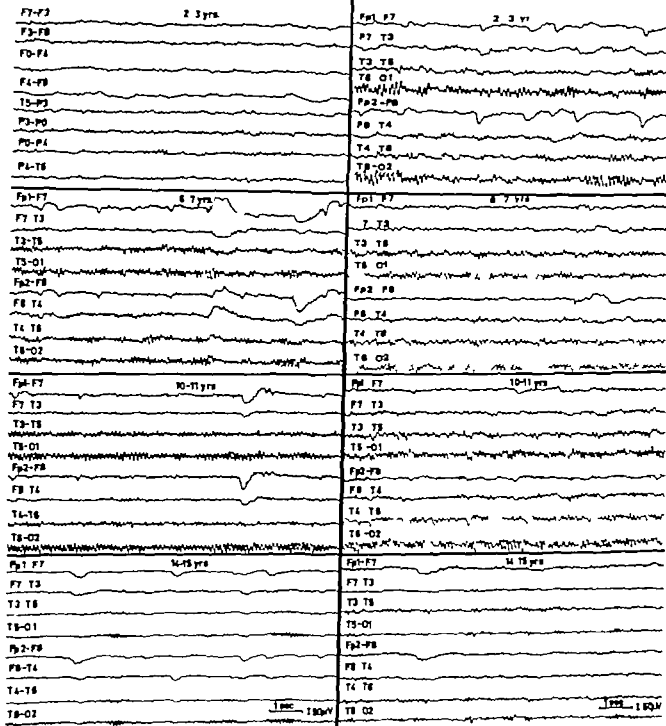


Fig. 1 Under heading "SUPERNORMAL" EEG are illustrated records with minimum of low frequency activity in different age groups; under heading "NORMAL" EEG are illustrated records with "normal" amount of low frequency activity in each of these age groups. (Figure from paper I)

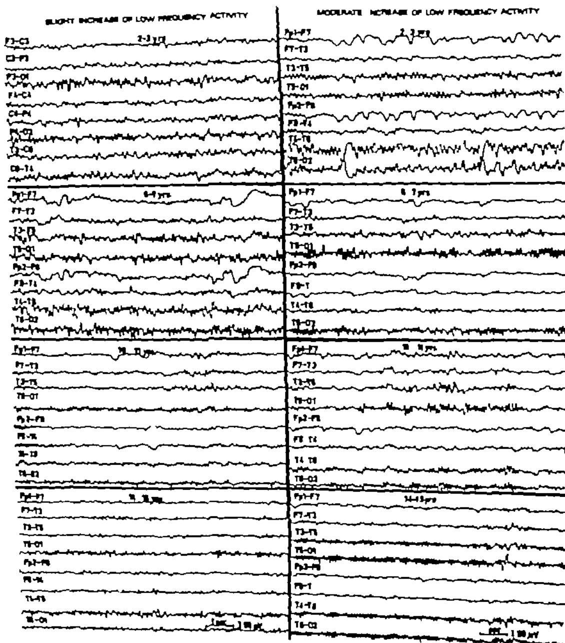


Fig. 2. Slight and moderate increase of low frequency activity (SIL and MIL) in different age groups. (Figure from paper I.)

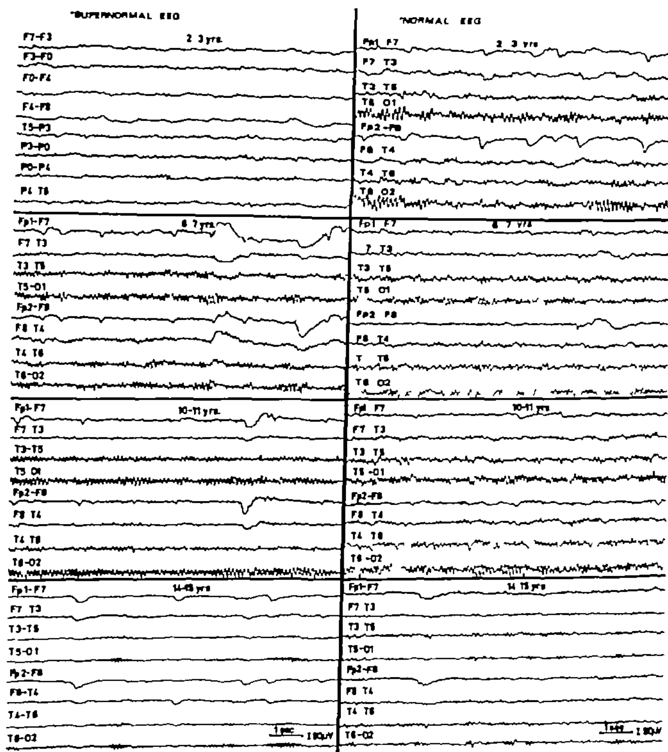


Fig 1 Under heading "SUPERNORMAL" EEG are illustrated records with minimum of low frequency activity in different age groups under heading "NORMAL" EEG are illustrated records with "normal" amount of low frequency activity in each of these age groups. (Figure from paper I)

Table III Patterns registered during analyses of EEG records in 928 children and adolescents 1 through 21 years.

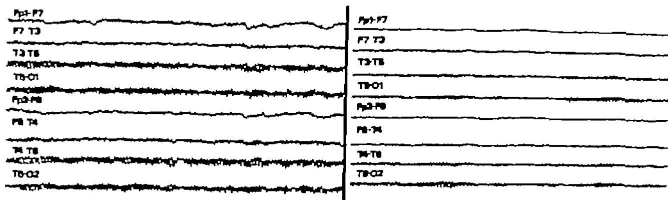
Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions; Comments
RESTING RECORD				
Alpha activity ( )		8—13	T—O	Hz, μV S, R
Beta activity (β)		14—30	Fr—C	Hz, μV I
Fast α-variant		16—24	T—O	I (only in the adolescent group)
Non-rhythmic				Hz, μV S, I
Theta activity (θ) Delta activity (δ)	Figs. 1 2, 3 Fig. 2	4—7 1—3	All derivations	amount f θ—δ — waves in relation to age: "Supernormal (minute = α-EEG" by Jung (40]) "Normal" (10—30 /o) SIL (slightly increased) MIL (moderately increased)
Rhythmic				
θ and δ-activity				Hz, μV S, R, I
Slow α-variant		4—6	T—O	Slow wave complexes in posterior derivations composed of two α-waves.
Polyphasic potentials		2—4	P—T—O	A polyphasic wave complex, with superpositioned α-activity, made up of an initial positive phase and following slow negative wave. An increase in the amplitude of the α-waves occurs during the first phase; sometimes, however this augmentation is valid only for single wave. During the second phase the amplitudes are reduced. The number of potentials were measured per 100 sec. (50 sec. in each of two montages).
Slow posterior rhythm (SPR)		2.5—4.5	P—T—O	Max. duration of episodes Quantity in per cent (duration of episodes in secs. in 200 sec. period; 100 sec. in each of two montages)
"Other rhythms		4—6	T (max.)	(Very like SPR)
Drowsy rhythms		(3—) 4—5 (3—) 4—5 5—6 6—7	Diffuse Diffuse with posterior accentuation (T) O P	

Abbreviations not explained elsewhere D = duration of episodes
I = incidence
R = Response to alerting stimulus
S = symmetry

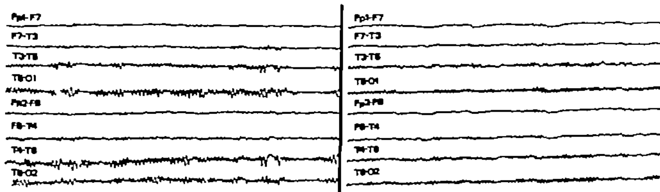
) *Patterns illustrated represent time-unit of 2 sec*

16 yrs 21 yrs

SUPERNORMAL EEG



NORMAL EEG



SLIGHT INCREASE OF LOW FREQUENCY ACTIVITY

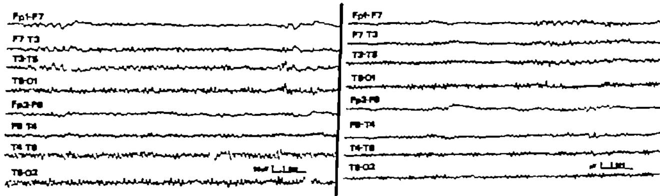


Fig. 3 Supernormal EEG, normal EEG and SIL in two subjects 16 and 21 years.
(Figure from paper IV)

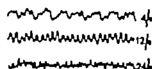
Table III Patterns registered during analyses of EEG records in 928 children and adolescents 1 through 21 years.

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed; Descriptions Comments
RESTING RECORD				
Alpha activity (α)		8—13	T—O	Hz, μV S, R
Beta activity (β)		14—30	Fr—C	Hz, μV I
Fast α-variant		16—24	T—O	I (only in the adolescent group)
Non-rhythmic				Hz, μV S, I
Theta activity (ϑ)	Figs. 1 2, 3	4—7	All derivations	amount of ϑ—δ — waves in relation to age: "Supernormal" (minute = "α-EEG by Jung [40]) "Normal" (10—30 /) SIL (slightly increased) MIL (moderately increased)
Delta activity (δ)	Fig. 2	1—3		
Rhythmic				
ϑ and δ-activity				Hz, μV S, R, I
Slow α-variant		4—6	T—O	Slow wave complexes in posterior derivations composed of two α-waves.
Polyphasic potentials		2—4	P—T—O	A polyphasic wave complex, with superponated α-activity made up of an initial positive phase and a following slow negative wave. An increase in the amplitude of the α-wa es occurs during the first phase; sometimes, however this augmentation is valid only for a single α-wave. During the second phase the amplitudes are reduced. The number of potentials were measured per 100 sec. (50 sec. in each of two montages).
Slow posterior rhythm (SPR)		2.5—4.5	P—T—O	Max. duration of episodes Quantity in per cent (duration of episodes in secs. in 200 sec. period 100 sec. in each of two montages)
"Other rhythms"		4—6	T (max.)	(Very like SPR)
Drowsy rhythms		(3—) 4—5	Diffuse	
		(3—) 4—5	Diffuse with posterior accentuation	
		5—6	(T) O	
		6—7	F	

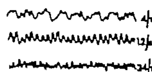
Abbreviations not explained elsewhere D = duration of episodes
I = incidence
R = Response to alerting stimulus
S = symmetry

*) *Patterns illustrated represent time-unit 1 2 sec*

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions Comments
Mu rhythm		7—11	T—C	Hz, μV S, I
Paroxysmal activity				Hz, μV S, I
Focal spikes or sharp-waves	F4-C4 C4-P4		All derivations	The number of spikes or sharp-waves occurring during a 6 min. period were counted, and an index of discharges per min. was devised, (also during sleep) *Spike* duration of 1/12 sec. or less. *Sharp wave* duration of more than 1/12 and less than 1/5 sec.
Equivocal focal spikes or sharp-waves	CO-C4 C4-T4 ↑			
Paroxysmal slow activity		3—7	All derivations focal or diffuse	High amplitude waves, sometimes of polyphasic character occuring in bursts.
HYPERVENTILATION				
Non-rhythmic low frequency activity		(2—) 4—7	P—T—O or diffuse	Hz, μV S, accentuated or arising, I (incl. dispersed polyph.poc.)
Rhythmic activity				Hz, μV^{1} S, P^{1} I
Anterior response		2—4	F	
Posterior response		2.5—4.5	P—T—O	Accentuated or arising SPR HV

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed; Descriptions Comments
Diffuse response		2—3 —7	Diffuse	
Paroxysmal activity		3—4	Diffuse	Hz, µV[2] S, P[3] I Bilat. synchr slow waves with a random poorly developed spike between the low waves.
				[2]) The amplitudes were estimated during the last 30 sec. of the activation procedure or as near this time as possible. The maximal amplitude was noted. [3]) Persistence (P) the time in sec., during which each effect persisted after termination of HV was counted.
INTERMITTENT PHOTIC STIMULATION				
Non-rhythmic low frequency activity		(2—) 4—7	T—O or diffuse	Hz, µV S, I (incl. dispersed *polyph. pot.*)
Photic driving		4—6—8— 11—15— 20—24 flashes/sec.	T—O	S, harmonics, subharmonics, I (determined in relation to rising course)

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions Comments
Mu rhythm		7—11	T—C	Hz, µV S, I
Paroxysmal activity				Hz, µV S, I
Focal spikes or sharp-waves	F4-C4 C4-P4		All derivations	The number of spikes or sharp-waves occurring during a 6 min. period were counted, and an index of discharges per min. was devised, (also during sleep) *Spike* duration of 1/12 sec. or less. *Sharp wave* duration of more than 1/12 and less than 1/5 sec.
Equivocal focal spikes or sharp-waves	CO-C4 C4-T4			
Paroxysmal slow activity		3—7	All derivations focal or diffuse	High amplitude waves, sometimes of polyphasic character occuring in bursts.
HYPERVENTILATION				
Non-rhythmic low frequency activity		(2—) 4—7	P—T—O or diffuse	Hz, µV S, accentuated or arising, I (incl. dispersed polyph.pot.)
Rhythmic activity				Hz, μV^1 S, P^a I
Anterior response		2—4	F	
Posterior response		2.5—4.5	P—T—O	Accentuated or arising SPR in HV

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions; Comments
Diffuse response		2—3 —7	Diffuse	
Paroxysmal activity		3—4	Diffuse	Hz, μV[1] S, P[2] I Bilat. synchr slow waves with random poorly developed spike between the slow waves.
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[1]) The amplitudes were estimated during the last 30 sec. of the activation procedure or as near this time as possible. The maximal amplitude was noted.

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Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions Comments
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Paroxysmal activity				Hz, µV S, I
Focal spikes or sharp-waves	F4-C4 C4-P4		All derivations	The number of spikes or sharp-waves occurring during a 6 min. period were counted, and an index of discharges per min. was derived, (also during sleep) *Spike* duration of 1/12 sec. or less. *Sharp wave* duration of more than 1/12 and less than 1/5 sec.
Equivocal focal spikes or sharp-waves	CO-C4 C4-T4 ↑			
Paroxysmal slow activity		3—7	All derivations focal or *diffuse*	High amplitude waves, sometimes of polyphasic character occuring in bursts.
HYPERVENTILATION				
Non-rhythmic low frequency activity		(2—) 4—7	P—T—O or diffuse	Hz, µV S, accentuated or arising, I (incl. dispersed polyph.poc.)
Rhythmic activity				Hz, µV S, P³ I
Anterior response		2—4	Fr	
Posterior response		2.5—4.5	P—T—O	*Accentuated or arising* SPR in HV

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed; Descriptions Comments
Paroxysmal activity				Hz, μV S, D I
Bilateral synchronous		2—5	Diffuse	Slow wa es with random, poorly developed spikes between the slow waves
Focal spikes or sharp-waves				
Equivocal focal spikes or sharp-waves				
14-6-PS		13—15	T(max.)	Hz, μV S, D, I
		5.5—7		Division according to the temporal relation between the appearance of the first burst and the first sleep spindle
Psychomotor variant		4—7	P—T—C	Hz, μV S, D, I *) saw-toothed waves **) flat-topped waves Most often seen during drowsiness and light sleep but also during waking state
6 H spike and -wave		4—7	T or diffuse	Hz, μV S, D I *) child and adolescent type **) adult type* The amplitude of the slow-wave component is always higher than that of the spike component. Seen during waking state as well as during drowsiness, light sleep, and I PHS.

Name	Appearance	Frequency range (Hz)	Main location	Parameters measured or assessed Descriptions Comments
Paroxysmal responses				Hz, μV S, D, I
Bilateral synchronous*		3—4	Diffuse	Paroxysmal responses at each flash frequency; amount of paroxysmal discharges for each 40-sec. period number of children with whom the test was discontinued
Bi-temporo-occipital		2—3	T—O	*) Slow waves (mainly children) or spike-and wave complexes (mainly adolescents and adults) **) Slow wave complexes of polyphasic character with an initial spike or spike-like component
Equivocal				
SLEEP				
Humps* Sleep spindles* K-complexes**	** ***			S According to criteria by Gibbs and Gibbs (27), Loomis *et al.* (49 50) Sparse humps noted in the adolescent group

The amount of *non-rhythmic low frequency activity* was classified as "minute" ("super normal" EEG), "normal (10—30 /s) "slightly" increased (SIL), and "moderately" increased (MIL) always related to age (Figs. 1 2) The corresponding percentual incidences were 0.8, 86, 12 and 1.3 per cent. Up to about 8 years the incidence of records with SIL was statistically significantly higher in boys than in girls in the 14 and 15 year-old children this condition was reversed (Fig. 5).

In children rhythmic low frequency patterns find their greatest expression. An exception to this is the *slow alpha variant* found in 3.5 per cent, which figure is low compared to the incidence of this rhythm in young persons and adults (cf paper IV). In children, however it can be difficult to differentiate the pattern from other low frequency patterns in posterior derivations.

Slow posterior waves or *polyphasic potentials* were found at a number of 1 to 67 per 100 sec. in 71 per cent — significantly more in older than in younger children, and significantly more often in girls than in boys. There was a pronounced skew distribution of polyphasic potentials, the median value being 5 per 100 sec. for girls, and 4 per 100 sec. for boys, while the corresponding mean values were 9 and 7 (Fig 6).

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In drowsiness four different rhythmic patterns were noted. *Diffuse rhythmic (3-) 4—5 Hz activity with or without posterior accentuation* appeared in 2.0 and 13 per cent respectively. The rhythmic activity with posterior accentuation was not found after the age of 8 years, while the first mentioned one disappeared a few years later. *Rhythmic 5—6 Hz activity in (temporo-) occipital derivations* was registered in only 0 4 per cent. The fourth "drowsy rhythm" is *6—7 Hz activity in anterior derivations* which occurred in 21 per cent, significantly more often in boys than in girls and significantly more in older than in younger children (Fig. 7)

Another sex linked rhythmic activity was the *mu rhythm* which was found in 7 1 per cent with a significant preponderance for girls, and significantly more with increasing age (Fig. 8). A positive correlation between this rhythm and focal paroxysmal activity at rest occurred.

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Non rhythmic low frequency activity in posterior derivations was the most common response to HV and occurred in 70 per cent. Rhythmic responses to HV were characterized according to their location as anterior posterior and diffuse effects.

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As regards persistence after terminated HV the anterior response persisted about 22 sec.,

frequency activity the preliminary results of the frequency analysis correlated significantly with the visual ones (20 52)

Statistical treatment[1]

Programming of the clinical and electroencephalographic material gave a total of 499 variables, of which 99 were quantitative and 400 qualitative Automatic data processing was performed on a SAAB D21 for plotting diagrams an IBM 1800 was employed. Selected variables were subjected to a correlation analysis The input for the correlation program was taken directly from a data tape Three different circumstances were specified in the correlation analysis

1 Both variables are quantitative.
2 One variable is quantitative and one is qualitative
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In the group of children, for one reason or another not all of the different types of clinical measurements or activations of EEG were carried out on all the individuals therefore a special coding system was used The characteristic was observed (1) the characteristic was not observed (0) the presence or absence of the characteristic could not be determined (—1)

Whenever *sex* was considered as a variable in the analyses, female (F) was coded *1*

In order to get a measure of the covariation between certain age dependent EEG variables and also some age dependent biological and clinical data, which was not influenced by a possible common age dependency the quantitative variables (alpha frequency alpha amplitude, body weight, body height, head circumference, and systolic and diastolic blood pressure) were measured in relation to mean values for the respective age group An examination of the graphic picture of the EEG variables development with age showed that these in certain cases were far from linear This is also seen in the very low values for the correlation with age, which were obtained. In these cases the non-linear functions were tested and a somewhat larger determination was obtained in the majority of cases with the second degree polynomial Alpha frequency and alpha amplitude have been presented as within the 95 per cent population control limits, which are obtained as 1 96 times the standard deviation of the residuals.

A combined analysis in the form of a multiple regression showed a somewhat higher determination which, however was still rather modest This points to an important random variation

A 5 per cent significance level has been employed in the analyses unless otherwise stated

RESULTS[2]

PAPER I: NON PAROXYSMAL ACTIVITY IN NORMAL CHILDREN 1 THROUGH 15 YEARS.

Resting record

The *alpha frequency* — mean 9.3 Hz (S.D 0 8) — increased linearly with age, girls showing higher frequencies than boys (Fig 4) The *alpha amplitude* — mean 56 μV (S.D 20) — increased up to a maximum figure at 6—9 years of age and thereafter declined. Asymmetry of the alpha amplitude, usually with lower amplitudes on the left, was noticed in 5 per cent.

The *beta amplitudes* usually amounted to 10—20 μV In 4 girls and 2 boys, however amplitudes up to 50 μV were seen, while in one girl and one boy the amplitudes measured amounted to 100 μV

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[1] In collaboration with L. H Imberg, fil. lic., Dept. of Statistics, University of Göteborg Sweden.

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As regards persistence after terminated HV the anterior response persisted about 22 sec.,

the posterior rhythmic as well as non rhythmic response about 47 sec. the diffuse delta response about 37 sec., and the diffuse theta response about 27 sec.

The only significant finding as regards HV effects in relation to sex was that girls showed more positive responses to HV than boys.

Intermittent photic stimulation

The response to I PH.S was divided in appearance of *low frequency activity* which occurred in 8 9 per cent and type of *photic driving* The incidence of low frequency activity showed a maximum at 4—5 years. Low frequency flicker responses (photic driving at 4 and 6 flashes/sec.) were found significantly more often in younger than older children while high frequency flicker responses (photic driving at 11 15 20 and 24 flashes/sec.) were found significantly more often in older than younger children (Fig 10) Significantly more girls than boys responded to I PH.S

Sleep

As regards sleep activation *spontaneous sleep* was achieved in 29 per cent — children younger than 9 years showing a higher incidence of spontaneous sleep than older children Despite barbiturate-induction 6.3 per cent of the children investigated could not fall asleep In girls this finding was significantly positively correlated to blood pressure, which may be partly dependent on so called "adrenalin arousal"[14]

Maturational factors are suggested to be of basic importance for many of the EEG patterns found To determine whether or not the observed EEG findings represent normal EEG as they are recorded in normal children a longitudinal study with serial EEG examinations in normal children as well as a psychological study of these children is in progress.

PAPER II: PAROXYSMAL ACTIVITY IN NORMAL CHILDREN 1 THROUGH 15 YEARS

The observed paroxysmal findings are described in Table IV Under 10 years of age there was a prevalence for paroxysmal activities appearing during drowsiness and light sleep while from 10 years onwards, the prevalence was for paroxysmal responses to I.PH.S There was a statistically significant positive correlation between age and paroxysmal responses to I PH.S only for girls. A statistically significant curvilinear correlation to age with preponderance for lower ages was observed regarding diffuse bilateral synchronous activity during drowsiness and light sleep

In girls the incidence of paroxysmal responses to I PH.S was significantly higher than in boys.

The total number of paroxysmal effects, excluding psychomotor variant pattern and 6 Hz spike-and wave phenomenon, was 130 distributed amongst 109 children or 15 per cent. There was no significant age or sex difference (Fig 12)

Table IV Percentual incidence of different paroxysmal phenomena including psychomotor variant pattern and 6 Hz spike-and wave phenomenon in 743 females and males aged 1 through 15 years.

	F	M	F+M
Paroxysmal findings at rest			
Focal spikes or sharp-waves	2.1	1.7	1 9
Focal spike-like (equivocal) activity	1.0	—	0.5
Paroxysmal slow activity	0.5	—	0.3
Paroxysmal findings during HV	0.3	0.3	0.3
Paroxysmal findings during I.PH.S			
Bilateral synchronous and diffuse	3.5	0.7	2.1
Bi temporo-occipital	5.4	2.8	4 1
B lat. synchr diff + + Bi-temp.-occ.	2.8	1.0	2.0
Equivocal	0.9	0.7	0.8
Paroxysmal findings during sleep			
Bilateral synchronous and diffuse	7.3	8.5	7 9
Focal spikes or sharp-waves	—	0.4	0.[illegible]
Equivocal do.	0.3	1 1	0.7
Psychomotor variant pattern	0.8	0.8	0.8
6 Hz spike-and wave phenomenon	—	0.3	0.1

The pathophysiology of paroxysmal phenomena is discussed. The results of the study may imply that maturational factors are responsible for the occurrence of the paroxysmal effects, which possibly have a subcortical origin. The accomplishment of a longitudinal investigation seems necessary in order to either confirm this hypothesis or to show other root causes. Such a study is in progress.

PAPER III 14-6-PS IN NORMAL CHILDREN 1 THROUGH 15 YEARS

The 14-6-PS is observed in 9.2 per cent as "14-6" (records with only typical or both typical and equivocal complexes), and in 7.0 per cent as "14-6?" (records with only equivocal complexes). The total incidence thus amounts to 16.2 per cent. "14-6" and "14-6?" were found to be related in several respects and were mostly dealt with as one variable ("14-6-Tot."). There was a statistically significant positive correlation between the incidence of 14-6-PS and age. A tendency toward levelling was seen from around the age of 13 years (Fig. 11). No significant sex differences were found. The importance of getting the child to the right stage of light sleep and maintaining him there must be heavily stressed.

The mean frequency of the fast component was 14 Hz and the mean frequency of the slow component 6.5 Hz. Only the fast component was found in 6.5 per cent, only the slow component in 23 per cent, while both components were noticed in 71 per cent.

The mean peak to peak amplitude of the 14-6-PS was 65 μV (S.D. ±15).

The 14-6-PS appeared most distinctly in bi-temporal derivations. Right occurrence or right preponderance was observed in 57 per cent.

In 96 per cent of the children showing 14-6-PS the pattern appeared within 5 minutes of light sleep — in 43 per cent already in deep drowsiness. The time relation between the appearance of the first sleep *spindle* and the first 14-6-PS burst was estimated, and a decay curve was constructed. The empirically obtained numbers of individuals remaining to show the 14-6-PS follow a curve of the same shape as the theoretical one.

A significant positive correlation was found between the occurrence of "14-6" or "14-6-Tot." and SIL for boys. A significant positive correlation was also observed between "14-6?" and bi-temporo-occipital paroxysmal response to I.P.H.S. in girls. A third significant positive correlation occurred between "14-6-Tot." and diffuse bilateral synchronous paroxysmal activity during drowsiness and light sleep. The incidence of "14-6-Tot." was also significantly positively correlated to the total incidence of paroxysmal activity (psychomotor variant pattern and 6 Hz spike-and-wave phenomenon excluded) as well as to equivocal paroxysmal effects.

The origin of the 14-6-PS is discussed. The positive correlations between 14-6-PS and paroxysmal phenomena, and the resemblance between the "maturational" development of the alpha rhythm and the 14-6-PS probably suggest that 14-6-PS is due to underlying thalamo-cortical mechanisms.

PAPER IV THE EEG IN NORMAL ADOLESCENTS 16 THROUGH 21 YEARS

Resting record

The *alpha frequency* showed a small, not statistically significant, augmentation during this 6-year age span; no sex difference was obtained. The mean frequency was 10.2 Hz (S.D. 0.9). The *alpha amplitude* showed a mean value of 56 μV (S.D. 24). Amplitudes of 20 μV or less occurred in 3 per cent; in 1 per cent if only records where the amplitude, during activations also did not exceed 20 μV are considered. Asymmetry of the alpha amplitudes with lower amplitudes on the left was noticed in 8 per cent, while lower amplitudes on the right were found in 5 per cent. The amount of *beta activity* was estimated but especially noted only if there was minute or

ample amount. Minute amount was found in 22 per cent and statistically significantly more often in males than in females. The mean beta amplitude was 11 μV (S D 7) with *significantly higher amplitudes* among females than males. Fast alpha variant with frequencies within the beta range was observed in 7 females (3 8 %)

The amount of *non rhythmic low frequency activity* was classified as minute (supernormal" EEG) "normal (10—15 %) slightly increased (SIL) and "moderately" increased (MIL) always related to age (Fig 3) The incidences were 8 1 87 4.3, and 0.5 per cent respectively The incidence of SIL+MIL was significantly higher in females than in males.

Some rhythmic patterns were observed at rest. *Slow alpha variant* was found in 28 per cent. Slow posterior waves or *polyphasic potentials* occurred at numbers of 1 to 18 per 100 sec. in 52 per cent. There was a rather evident skew distribution — the median value being 1 polyphasic potential per 100 sec., while the mean value was 2. No sex difference was found.

In drowsiness *rhythmic 5—6 Hz activity in (temporo-)occipital derivations* occurred in 2 7 per cent. A higher incidence was found for *rhythmic 6—7 Hz activity in anterior derivations* — 27 per cent — without sex difference *Mu rhythm* appeared in 6.5 per cent without sex difference.

In one 17 year-old girl (0 5 %) *rhythmic 4—5 Hz activity in posterior derivations* appeared this rhythm showed similarities to the typical child rhythm" called SPR.

Hyperventilation

The degree of HV was estimated as slight (2 0 %) moderate (45 %) and strong (53 %) *Non rhythmic low frequency activity in posterior derivations* was the most common response to HV and observed in 69 per cent. The rhythmic responses to HV were characterized according to their location as anterior or diffuse effects.

Rhythmic 2—4 Hz activity in anterior derivations was registered in 11 per cent, while *rhythmic diffuse 2—7 Hz activity* was seen in 30 per cent. The last mentioned activity consisted of either only delta waves (3.8 %), only theta waves (20 %) or a combination of these (6.5 %)

As regards persistence after terminated HV delta activity persisted about 15 sec. and theta activity about 24 sec. The non rhythmic posterior activity persisted about 50 sec.

Lack of response to HV was significantly more common in ages over than under 19 years in females. More than one response to HV was significantly more common in ages under than over 19 years.

Intermittent photic stimulation

The response to I PH.S was divided into occurrence of *low frequency activity* which was noted in 29 per cent, and type of *photic driving* Low frequency flicker responses (photic driving at 4 and 6 flashes/sec.) were found in 8 1 per cent, while high frequency flicker responses (photic driving at 11 15 20 and 24 flashes/sec.) were found in 81 per cent. There were *no significant age or sex differences* As regards high frequency responses females showed a tendency for the higher ones and males a tendency for the lower ones within this range.

Sleep

Spontaneous sleep was achieved in 63 per cent. The occurrence *of humps* was noted if in a scanty amount. This was seen in 8 6 per cent of the subjects.

Paroxysmal activity (14-6-PS, psychomotor variant pattern, and 6 Hz spike-and wave phenomenon excluded) were found in 4 9 per cent of the subjects. at rest in 1.6 per cent, during LPHS in 2.7 per cent, and during sleep in 1.6 per cent. One female and one male presented paroxysmal effects during both LPHS. and sleep Most paroxysmal ef fects occurred sporadically and were of an equivocal character There was no significant age or sex relation.

The 14-6-PS was found in 14.6 per cent either as 14-6" (4 9 %) or "14-6?" (9.7 %). The bursts appeared sporadically and with short duration. The mean peak to peak amplitude was 45 μV (S.D 13). Right occurrence or right preponderance was observed in 67 per cent. No age or sex relation was found.

Psychomotor variant pattern was noticed in 1 1 per cent and *6 Hz spike-and-wave phenomenon* in 3.8 per cent.

In comparison with normal children there are fewer differences in regard to age and sex in normal adolescents. This may be an expression for a tapering off of a maturational process.

GENERAL RESULTS

As was stated in the introduction one of the purposes of this investigation was to describe the EEG findings in relation to age and sex. So far the results for children and young persons have been delineated separately but some of the EEG findings can be studied to advantage over the total age span, i. e. from the age of 1 through 21 years. In this context it is not the numerical incidence of different variables which is of interest, but the relations between these variables and age and sex respectively Once and for all in this study it will be stated that there were no significant correlations between handedness and EEG variables.

Table V shows statistically significant age and sex dependent variables for the group of individuals who had entered or passed puberty (311 subjects) and for the total material (928 subjects) For purposes of comparison the child group (743 subjects) is also included.

Resting record

The *alpha frequency* shows a successive slight augmentation with age (Fig. 4) According to the regression equation $y = 7\,980 + 0.174\ X - 0\,003\ X^2$ the increase (dy) in frequency during the second year of life is 0 17 Hz, while the increase during the twenty-second year is 0.11 Hz. If an extrapolation is made to find the age where the increase terminates and the alpha frequency starts to decline, this will appear at 58 years.

Females showed a higher alpha frequency throughout the difference, however being in the order of tenths.

The occurrence of *non-rhythmic low frequency activity* showed a characteristic age development as described in papers I and IV As regards SIL this is illustrated in Fig 5 The course during the first 7 years will be discussed later Fig 5 also shows the difference in incidence between females and males with SIL males presented a higher incidence up to and including 8 years of age and a lower incidence from 14 years of age, with a varying pattern in the intervening ages.

Rhythmic patterns showing relations to age and sex were *polyphasic potentials* (Fig 6), *6—7 Hz activity in anterior derivations during drowsiness (Fig. 7)*, and *mu rhythm* (Fig. 8)

The incidence of the number of polyphasic potentials per 100 sec. increases slowly to reach a maximal level around 9—12 years for males, the females showing this level about two years earlier Females also have significantly more polyphasic potentials than males up to about 8 years. From around 11 years of age the incidence declines. During this period the incidence in regard to sex varies.

Table V Statistically significant correlations between some variables and age or sex in 743 children, in the 311 individuals who were post pubertal, and in 928 individuals aged 1 through 21 years.

	AGE			SEX		
	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.
Alpha frequency (Hz)	+	+	+	F		F
"Normal" EEG { L > R	+		+			
"Normal" EEG { R > L			+			
"Supernormal" EEG		+				
SIL	+	−			F	
Slow alpha variant		+	+			
Polyphasic potentials/100 sec.	+	−	−	F		F
SPR	−					
Diff rhythmic (3—) 4—5 Hz act. with/without post-acc. during drowsiness	−					
Rhythmic 6—7 Hz activity in anterior derivations during drowsiness	+	+	+	M		M
Mu rhythm	+		+	F		F
No response to HV		+	+	M		
2—4 Hz activity in anterior derivations during Hv	+	−	+			
SPR during HV	−					
Diffuse 2—7 Hz activity during HV	+	−	−			
No response to I.PHS.	−		−	M		M
Non rhythmic low frequency activity during I.PHS.		+	+			
Photic driving { No	−		−	M		M
Photic driving { → 4 → 6/sec.	−		−			
Photic driving { →11 → 15/sec.	+	−	+			
Photic driving { →20 → 24/sec.		+				
Photic driving { →≥11/sec		+			M	
Spontaneous sleep	−	+	+		M	
14-6-PS	+		+			
Paroxysmal activity		−	−		F	F
Systolic blood pressure	+			F		
Diastolic blood pressure	+			F	F	F
Syncope	+	+	+			F

Symbols in bold face equal 1 per cent significance level. For abbreviations see page 4

Hz Alpha frequency

Age in years

Fig. 4 *Alpha frequency* in relation to age in the total material (continuous line). The diagram is based on 2nd degree polynomial. The dot-dash lines indicate 95 per cent population control limits. The mean values of each age group (dots and crosses) are indicated. In this fig. as well as in figs. 5, 6, 7, 8, 9, 11, and 12 the corresponding curves (broken lines) for the child group are inserted (see papers I, II, and III).

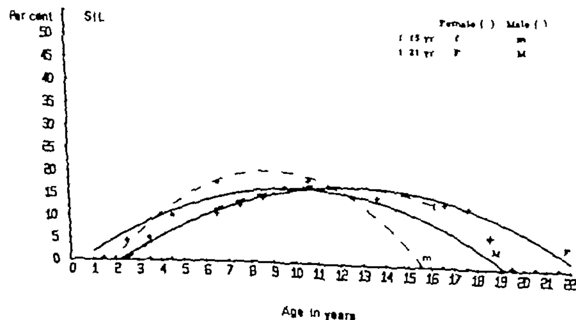


Fig. 5 Incidence of slight *[illegible] / low frequency activity (SIL)* in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age ------ (dots and crosses) are indicated. See also legend to *fig. 4*

Table V Statistically significant correlations between some variables and age or sex in 743 children, in the 311 individuals who were post-pubertal, and in 928 individuals aged 1 through 21 years.

	AGE			SEX		
	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.
Alpha frequency (Hz)	+	+	+	F		F
"Normal" EEG { L > R	+		+			
"Normal" EEG { R > L			+			
"Supernormal EEG		+				
SIL	+	−			F	
Slow alpha variant		+	+			
Polyphasic potentials/100 sec.	+	−	−	F		F
SPR	−					
Diff rhythmic (3—) 4—5 Hz act. with/without post.acc. during drowsiness	−					
Rhythmic 6—7 Hz activity in anterior derivations during drowsiness	+	+	+	M		M
Mu rhythm	+		+	F		F
No response to HV		+	+	M		
2—4 Hz activity in anterior derivations during Hv	+	−	+			
SPR during HV	−					
Diffuse 2—7 Hz activity during HV	+	−	−			
No response to I PH.S.	−		−	M		M
Non rhythmic low frequency activity during I.PH.S		+	+			
Photic driving { No	−		−	M		M
Photic driving { → 4 → 6/sec	−		−			
Photic driving { →11 → 15/sec.	+	−	+			
Photic driving { →20 → 24/sec.		+				
Photic driving { →≥11/sec		+			M	
Spontaneous sleep	−	+	+		M	
14-6-PS	+		+			
Paroxysmal activity		−	−		F	F
Systolic blood pressure	+			F		
Diastolic blood pressure	+			F	F	F
Syncope	+	+	+			F

Symbols in bold face equal 1 per cent significance level. For abbreviations see page 4

Hz Alpha frequency

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 0.5 0.0

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Age in years

Fig. 4 *Alpha frequency* in relation to age in the total material (continuous line). The diagram is based on 2nd degree polynomial. The dot-dash lines indicate 95 per cent population control limits. The mean values of each age group (dots and crosses) are indicated. In this fig. as well as in figs. 5, 6, 7, 8, 9, 11 and 12 the corresponding curves (broken lines) for the child group are inserted (see papers *I*, *II*, and *III*).

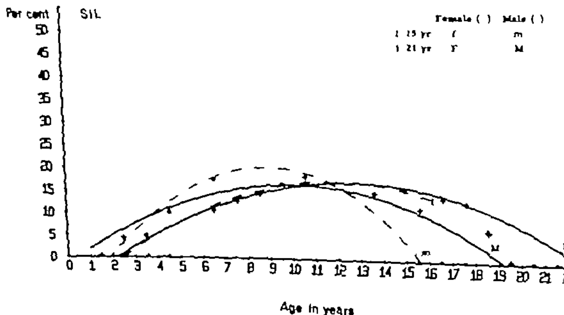


Fig. 5 Incidence of *slight increase of low frequency activity (SIL)* in relation to age in 483 normal femal[e] and 443 normal males. The curves ar[e] based on 2nd degree polynomials. The percentual incidence in each ag[e] group (dots and crosses) are indicated. See [a]lso legend to fig. 4

Table V Statistically significant correlations between some variables and age or sex in 743 children, in the 311 individuals who were post pubertal, and in 928 individuals aged 1 through 21 years.

	AGE			SEX		
	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.	1—15 yrs.	Puberty —21 yrs.	1—21 yrs.
Alpha frequency (Hz)	+	+	+	F		F
"Normal EEG L > R	+		+			
"Normal EEG R > L			+			
"Supernormal EEG		+				
SIL	+	−			F	
Slow alpha variant		+	+			
Polyphasic potentials/100 sec.	+	−	−	F		F
SPR	−					
Diff rhythmic (3—) 4—5 Hz act. with/without post.acc. during drowsiness	−					
Rhythmic 6—7 Hz activity in anterior derivations during drowsiness	+	+	+	M		M
Mu rhythm	+		+	F		F
No response to HV		+	+	M		
2—4 Hz activity in anterior derivations during Hv	+	−	+			
SPR during HV	−					
Diffuse 2—7 Hz activity during HV	+	−	−			
No response to I PH.S	−		−	M		M
Non rhythmic low frequency activity during I.PH.S		+	+			
Photic driving: No	−		−	M		M
Photic driving: → 4 → 6/sec.	−		−			
Photic driving: →11 → 15/sec.	+	−	+			
Photic driving: →20 → 24/sec		+				
Photic driving: →≥11/sec.		+			M	
Spontaneous sleep	−	+	+		M	
14-6-PS	+		+			
Paroxysmal activity		−	−		F	F
Systolic blood pressure	+			F		
Diastolic blood pressure	+			F	F	F
Syncope	+	+	+			F

Symbols in bold face equal 1 per cent significance level. For abbreviations see page 4

Fig. 4. *Alpha frequency* in relation to age in the total material (continuous line). The diagram is based on 2nd degree polynomial. The dot-dash lines indicate 95 per cent population control limits. The mean values of each age group (dots and crosses) are indicated. In this fig. as well as in figs. 5, 6, 7, 8, 9, 11, and 12 the corresponding curves (broken lines) for the child group are inserted (see papers I, II, and III).

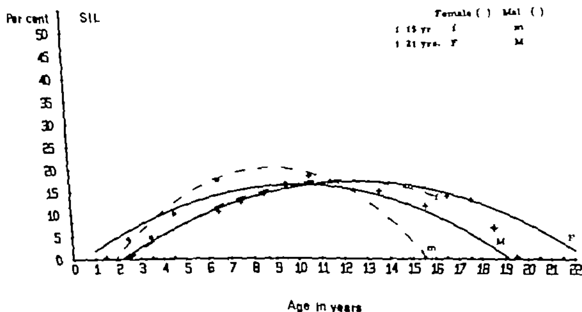


Fig. 5. Incidence of *slight increase of low frequency activity (SIL)* in relation to age in 483 normal females and 443 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age group (dots and crosses) are indicated. See also legend to *fig. 4*

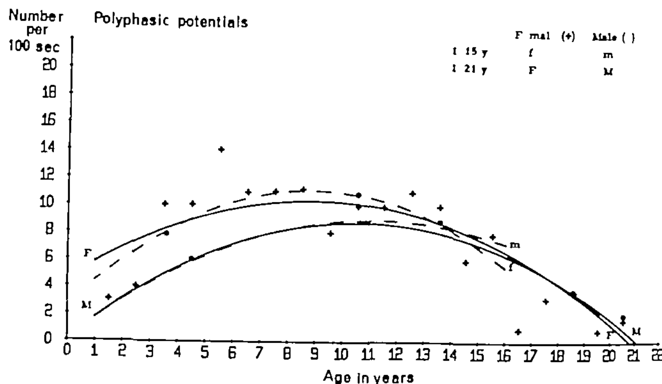


Fig. 6. Number of *polyphasic potentials* per 100 sec. in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The mean values of each age group (dots and crosses) are indicated. See also legend to fig. 4

Per cent
6–7 Hz anterior rhythm
Femal (+) Mal ( )
1 15 y f m
1 21 y F M
Age in years

Fig. 7 Incidence of *6—7 Hz anterior rhythm* in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age group (dots and crosses) are indicated. See also legend to fig. 4

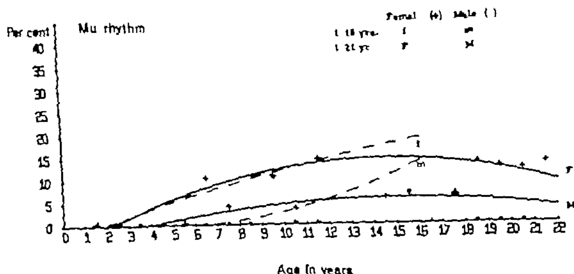


Fig. 8. Incidence of mu rhythm in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age group (dots and crosses) are indicated. See also legend to Fig. 4

The 6—7 Hz anterior rhythm during drowsiness is a mainly "male pattern" from 4 years onwards, a statistically significant preponderance for males being found for children as well as the total material, but not for the post-pubertal group. For males there is a maximal incidence of the pattern in the early teens, whereupon a slow decline is seen. Females showed an increasing tendency throughout the age period investigated.

The incidence of mu rhythm in the child group showed an increasing course in relation to age. If however the total number of individuals is considered, the course of the incidence of mu rhythm in relation to age shows a maximal level in the early teens with a later slow decline. The mu rhythm is a mainly female pattern the significant preponderance for females as found in both the child group and the total material was, however not seen in the post-pubertal group

The female preponderance for polyphasic potentials and mu rhythm, as well as the male preponderance for 6—7 Hz activity is in accord with the results in paper I, and thus mainly depends on the conditions in childhood.

Hyperventilation

The ability to respond with EEG changes at HV increased from the age of 3 years and reached a maximal level around 9—11 years of age whereupon there was a successive decline. As regards the *diffuse rhythmic responses* to HV the incidence in relation to age mainly follow the same course as was found for the child group (Fig. 9). The peak incidence for appearance of diffuse response to HV falls around 9—12 years.

The incidence at HV of *non-rhythmic low frequency activity in posterior derivations follows* a course similar to the one concerning diffuse responses. SPR during HV was not found in the adolescent group. This led to an extension of the parabolic curve, which represented the incidence of the pattern concerned in relation to age up to 16 years. For the total material then, SPR at HV appears with successively declining incidence. The *anterior response* to HV increases in incidence slowly up to 14—16 years of age, whereupon a slow decline occurs. If only ages up to 16 years were investigated a nearly linear increase in incidence appeared.

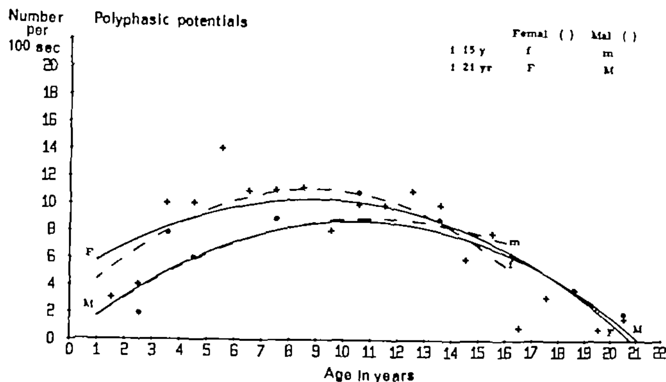


Fig. 6. Number of *polyphasic potentials* per 100 sec. in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The mean values of each age group (dots and crosses) are indicated See also legend to fig. 4

Per cent

6-7 Hz anterior rhythm

Femal (+) Mal ( )

1 15 yrs f m

1 21 yr F M

Age in years

Fig 7 Incidence of *6—7 H anterior bythm* in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age group (dots and crosses) are indicated. See also legend to fig. 4

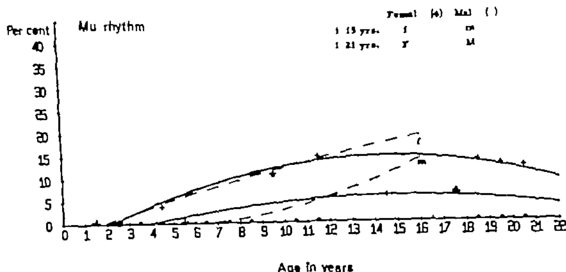


Fig. 8. Incidence of mu rhythm in relation to age in 483 normal females and 445 normal males. The curves are based on 2nd degree polynomials. The percentual incidence in each age group (dots and crosses) are indicated. See also legend to fig. 4

The 6—7 Hz anterior rhythm during drowsiness is a mainly "male pattern" from 4 years onwards, a statistically significant preponderance for males being found for children as well as the total material, but not for the post pubertal group. For males there is a maximal incidence of the pattern in the early teens, whereupon a slow decline is seen. Females showed an increasing tendency throughout the age period investigated.

The incidence of mu rhythm in the child group showed an increasing course in relation to age. If however the total number of individuals is considered, the course of the incidence of mu rhythm in relation to age shows a maximal level in the early teens with a later slow decline. The mu rhythm is a mainly "female pattern" the significant preponderance for females as found in both the child group and the total material was, however not seen in the post pubertal group.

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The incidence at HV of *non-rhythmic low frequency activity in posterior derivations* follows a course similar to the one concerning diffuse responses. *SPR* during HV was not found in the adolescent group. This led to an extension of the parabolic curve, which represented the incidence of the pattern concerned in relation to age up to 16 years. For the total material then, SPR at HV appears with successively declining incidence. The *anterior response* to HV increases in incidence slowly up to 14—16 years of age, whereupon a slow decline occurs. If only ages up to 16 years were investigated a nearly linear increase in incidence appeared.

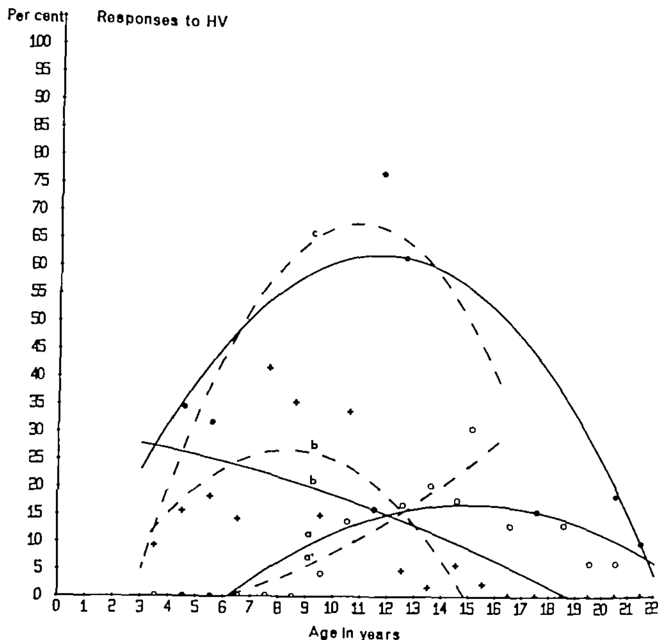


Fig 9 Incidence of *response t HV* obtained, *a* in anterior derivations, *b* in posterior derivations, and *c* dif fusely in relation to age in 799 normal children and adolescents. Each curve is based on a 2nd degree poly nomial. The percentual incidence in each age group (for *a* open circles, for *b* crosses, and for *c* dots) are indi cated. See also legend to Fig 4 (regarding th curves a b and c')

Intermittent photic stimulation

As regards I.PH.S the decrease in incidence of low frequency photic driving and the in crease in high frequency photic driving showed the same trend throughout the investigated age period (Fig 10) An augmentation how ever of the incidence of high frequency photic driving and a corresponding reduction in low frequency photic driving occurred around 8—12 years of age — females showing this change about 1 year before the males.

Sleep

Sleep has been studied concerning the differ ence between spontaneous sleep and barbi turate-induced sleep in relation to different EEG variables and clinical as well as biologi cal data. Sleep was also studied with regard

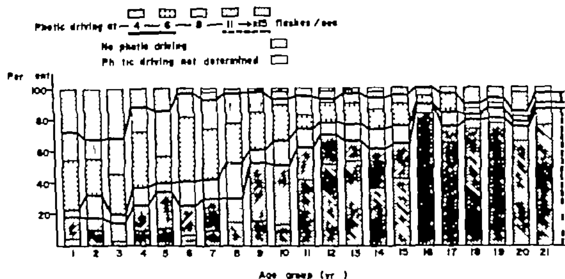


Fig. 10. *Photic driving* for different flash frequencies in 790 normal children and adolescents divided in age groups. The course of "low frequency" and "high frequency" photic driving has been indicated.

Per cent 14 6 PS

55 50 45 40 35 30 25 20 15 10 5

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Age in years

Fig. 11. Incidence of *14-6-PS* in relation to age in 783 normal children and adolescents. The curve is based on 2nd degree polynomial. The percentual incidence in each age group has been indicated (dots). See also legend to fig. 4

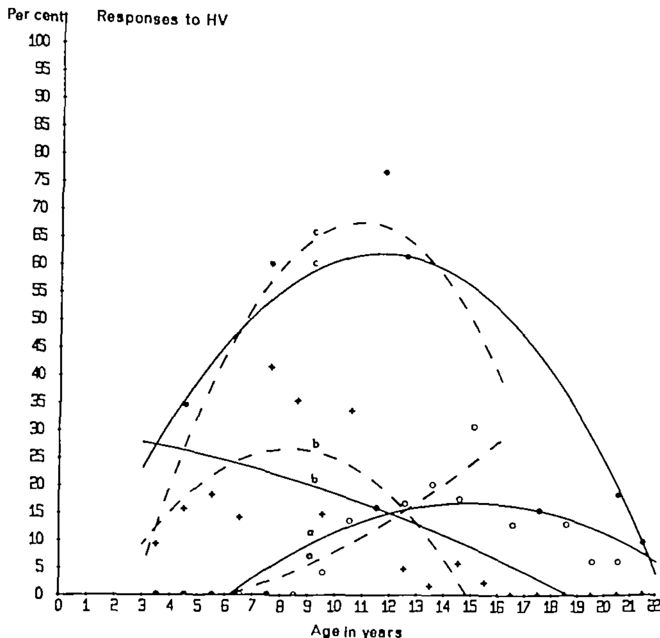


Fig 9 Incidence of *response to HV* obtained, *a* in anterior derivations, *b* in posterior derivations, and *c* diffusely in relation to age in 799 normal children and adolescents. Each curve is based on a 2nd degree polynomial. The percentual incidence in each age group (for *a* open circles, for *b* crosses, and for *c* dots) are indicated See also legend to fig 4 (regarding the curves a b and c')

Intermittent photic stimulation

As regards I PH.S the decrease in incidence of low frequency photic driving and the increase in high frequency photic driving showed the same trend throughout the investigated age period (Fig 10) An augmentation, however of the incidence of high frequency photic driving and a corresponding reduction in low frequency photic driving occurred around 8—12 years of age — females showing this change about 1 year before the males.

Sleep

Sleep has been studied concerning the difference between spontaneous sleep and barbiturate-induced sleep in relation to different EEG variables and clinical as well as biological data. Sleep was also studied with regard

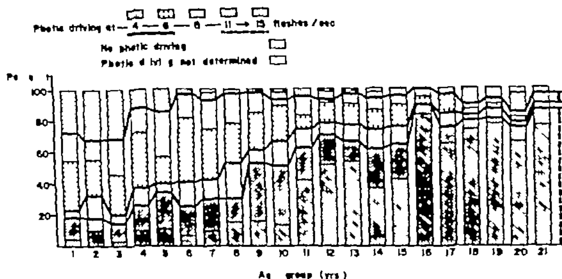


Fig. 10 *Photic driving* for different flash frequencies in 790 normal children and adolescents divided in age groups. The course of "low frequency" and "high frequency" photic driving has been indicated.

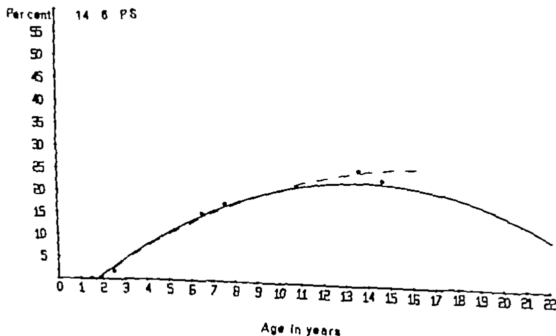


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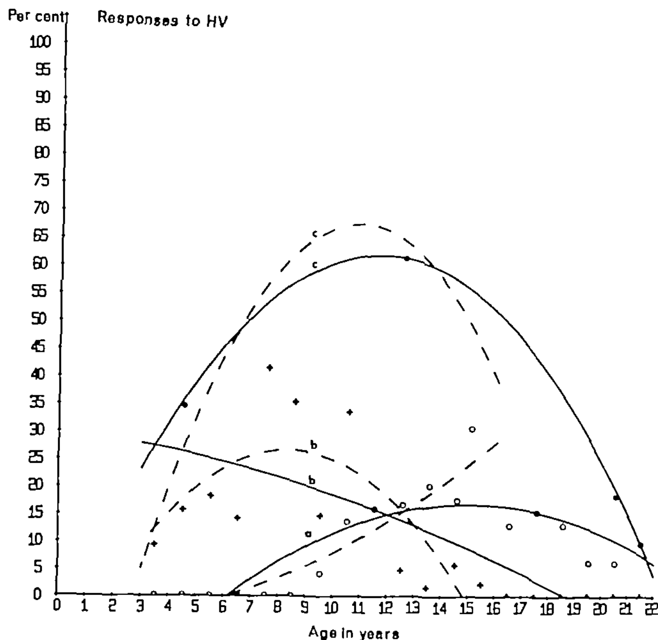


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Table VI Significant positive (+) and negative (−) correlations between different EEG variables in children ○ (1—15 years), adolescents △ (16—21 years), and the total group □ (1—21 years).

	Resting record: α Hz	α μV	SIL	Slow α var	Polyphas pot/100	SPR	Diffuse 3—5 H (drowsy)	Anterior 6—7 H (drowsy)	M	HV: Diffuse 2—7 Hz	I.P.H.S. Photic dri. →4 →6 fl./s.	I.P.H.S. Photic dri. →11 →≥15 fl./s.	Sleep: 14-6 PS
V	⊟												
SIL	⊟	△+											
Slow variant	⊟	⊞	⊕										
Polyphas. pot./100 sec	⊟	⊞	⊞										
SPR	⊖		⊕	⊕	⊖								
Diffuse 3—5 Hz (drowsy)	⊖		⊖		⊖	⊕							
Anterior 6—7 Hz (drowsy)	⊟	⊕	⊞										
M		⊞				⊖							
Diffuse 2—7 Hz in HV	△−		⊞	⊟	⊞	⊖							
Photic driving →4→6 flashes/sec.	⊟	⊞	△+	⊕	⊞			⊞	⊟				
Photic driving →11→≥15 flashes/sec.	⊞	⊖		⊖	⊟		⊖	⊟	⊞		⊟		
14-6-PS	△−	△+	⊞		△+			⊞		⊞		⊕	
Parox act.		⊞	⊞	△+	⊞	⊕		△+				⊟	⊞

In this context it can be mentioned that an EEG with no signs of SIL, MIL or paroxysmal phenomena recorded at rest as well as during activations, i.e. a *totally normal* EEG was noted for 68 per cent of the children while the corresponding figure for adolescents was 77 per cent, which difference is statistically significant.

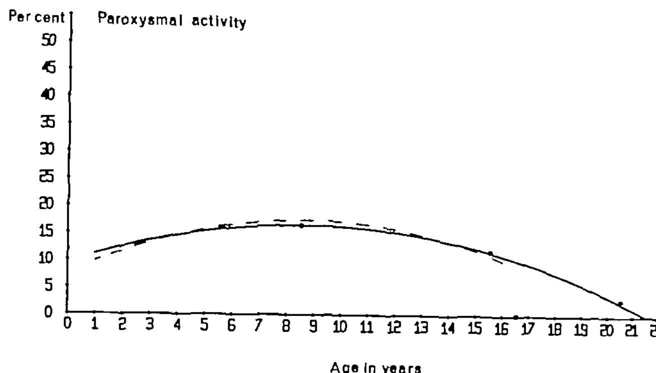


Fig. 12. Incidence of *paroxysmal activity* in relation to age in 928 normal children and adolescents. The curve is based on a 2nd degree polynomial. The percentual incidence in each age group has been indicated (dots). See also legend to fig. 4

to 14-6 PS paroxysmal effects, and in the adolescent group to the occurrence of sparse humps. The examination of sleep records was limited to these variables, because another report will concern studies of different sleep stages, for example paradoxical sleep (rapid eye movement sleep or REM sleep)

Spontaneous sleep was easier to achieve in older than younger individuals. It was also found that the incidence of spontaneous sleep was higher in post pubertal males than females.

14-6 PS showed a maximal incidence in the early teens as described in paper III whereupon a slow decline was obvious (Fig 11)

Paroxysmal activity excluding 14-6-PS psychomotor variant pattern and 6 Hz spike-and wave phenomenon mainly consists of effects appearing in drowsiness and light sleep and during I PH.S., as was shown in paper II

The incidence of paroxysmal activity in relation to age is shown in Fig 12 Already during the first years of life there is an incidence of over 5 per cent. According to the polynomial a maximal incidence is found around 7—9 years of age, whereupon there is a successive decline. This curve, however seems to consist of two curves — one with a maximal incidence around 4—7 years of age, and one with a less apparent maximal incidence around 11—13 years of age The first mentioned phase is comparable to the paroxysmal responses to sleep activation while the last mentioned corresponds to the responses appearing during I.PH.S

The predominance for females as regards paroxysmal patterns was most apparent in the older age groups. Paroxysmal activity is one of the EEG variables studied which shows significant positive correlations to several variables especially of low frequency character This one along with some other interrelated variables, is shown in Table VI

included in the correlation analysis. In the child material only one significant correlation was found this was a positive correlation between alpha frequency and social group I The difference between the mean values for alpha frequency in social group I and the combined groups II and III, in this correlation was, however only 0.07 Hz. In the adolescent material or in the two materials taken together there were no significant correlations between social group and EEG variables. These findings led to the conclusion that no consideration should be taken in regard to social group in the analyses.

Other deviations from the general population relating to the strict selection are also found. There was a higher percentage married and a lower percentage divorced parents, as well as a lower number of first-born children in comparison with the general population (71). The differences in these factors between the child material and the adolescent material were not significant — the latter group resembling the general population more than the first one.

In view of the established aim for this investigation the total material can be regarded as composing an entity of a defined sample of normal children and adolescents for EEG examination. The common characteristics among these individuals will be more useful for the established purposes than if this investigation had been carried out among a cross-section of the population of the same ages, but taken only at random.

EEG method

In the present investigation there was an intent to perform recording at rest as well as during HV I.PHS., and sleep in each subject. This was achieved in 70—90 per cent of children from the age of 5 years (see paper I table II) and in all young persons with one exception as regards sleep activation. No investigation on "normal subjects, as far as is known by the author has earlier been published, where resting EEG and the aforementioned three activations were accomplished on the same material at such a high percentage as in the present study

EEG findings in relation to age

In papers I II and III the relation between age and incidence of different EEG variables has been illustrated by second degree polynomials. From the beginning of this study third degree polynomials were also calculated. The difference in determination between these polynomials, however was very small.

The *alpha frequency* showed a parabolic course only after the total material up to 22 years had been analysed the course during childhood, however seemed to be linear This is in accordance with findings by Bernhard and Skoglund (4 5) if only mean frequencies of 8—13 Hz in individuals from 1 year of age onwards are considered in their material. The augmentation of the alpha frequency slowly wanes towards middle age, as was also shown by Gibbs and Knott (31) The increase in alpha frequency up to the early twenties corresponds to the morphological growth of the brain, which is suggested to proceed throughout adolescence (76). This age dependency may be a reflection of the development of the neuronal connections underlying the rhythm-generating mechanisms parallel with other changes of the brain.

A factor of importance reflecting the developmental course with increasing age is the individual response to I.PH.S. by *photic driving* Photic driving of low frequencies, i.e. in this study for 4 and 6 flashes per sec., is most common in children up to about 9 years, whereupon there is a successive decrease in incidence. An increased incidence of *high* frequency photic driving, i.e. responses to 11 or more flashes per sec., occurs throughout the age span investigated but is most evident from about 9 years. Furthermore there is a higher incidence of photic driving for 20 and 24 flashes per sec., and a lower incidence of har

DISCUSSION

Definition and criteria of normality

The purposes of this investigation may be summarized as follows an attempt to achieve an increased understanding of the EEG characteristics of normal individuals in relation to age and sex and to get a model for normally existing EEG findings, which in clinical diagnostic work can be used in the evalutation of records from children and adolescents with neurological psychiatric, and other disorders.

To date there is no generally accepted definition for clinical conceptualization of normality Offer and Sabshin (58) have delineated four distinctive approaches, which are normality as health normality as utopia "normality as average and normality as process Karlberg (42) has discussed normality in relation to health" and has pointed out the difficulty of classifying adequately a body of people belonging to these categories "Normality" is essentially a synthesis of definitions based upon physical and psychological observations.

In the literature concerning EEG non-epileptic control subjects are usually used These are to a very great extent individuals with neurological or psychiatric disorders. In the present investigation only those subjects were included, which do not show signs and symptoms or present a history implying a risk for the appearance of EEG changes, which empirically are regarded as deviating and thus as pathological The employed criteria of normality have been considered in detail which as far as is known by the author has not been done in other investigations on the subject. Although the criteria of normality may seem rather stringent, there is, however no sharp limit between "normal" and "not normal individuals. With all other criteria of normality fulfilled subjects with mild nail biting and sporadic syncope, as well as children having parents or siblings with certain psychic complaints have been included in the investigation

Selection and representativeness

The subjects investigated were recruited from different vocational, social, and economic sources a single source cannot be considered a random sample for a study on normal individuals. The intent was also to recruit the subjects from different parts of Göteborg a Swedish city in rapid, dynamic development with about half a million inhabitants. For practical reasons, however the children were recruited from a part of the city with easy access by public transport to the laboratory at Sahlgrenska sjukhuset. The young persons came from all parts of the city and some of them were students living only temporarily in Göteborg The comparison between the distribution of social groups in the aforementioned part of Göteborg from which the children were recruited and the city as a whole does not show any differences, and this distribution also fairly represents Sweden.

The selection method of the present material resulted however in a skew social group distribution towards higher social groups. The reason for this is certainly multifactorial. Mental and somatic morbidity is higher in lower social groups in comparison with the other groups (34 39 41 51 57 72) This fact is probably of significance in the selection as is also the circumstance that low birth weight is related to lower social group (26, 76). Another factor which may have played a contributory role, in regard to the children, is deviation in the parents motivation to permit their children to participate in an EEG investigation. The young persons, however decided for themselves. This may be an explanation for the difference in the social group distribution between children and young persons. Neither in the child material nor in the adolescent material, was there any difference between the social groups as regards onset of puberty

In order to estimate the influence of the skew social grouping on the registered developmental EEG patterns, this factor was

appear at certain age levels without apparent antecedent growth from slower activity present at an earlier age. These rhythms may also later vanish without any change in frequencies. According to Ellingson (21) "phylogenetically more recent brain structures, which come to maturity later than more primitive structures, leap into action when they reach a certain point in maturation, masking and/or suppressing already active systems of earlier phylogenetic and ontogenetic maturity"

The only patterns still showing an evident surviving" tendency at the end of the investigated age span are the *rhythmic 6—7 Hz activity in anterior derivations during drowsiness* and *14-6-PS*. As regards 14-6-PS this has also been shown by Gibbs and Gibbs (29).

It can be suggested that the relation of different EEG variables to increasing age is *consistent with a common maturation process*, which is most evident from the ages around 9 years. As instances of it, EEG variables such as SIL, polyphasic potentials, delta responses to HV photic driving and paroxysmal activity are evident. The indications of maturation of various brain areas, as estimated from the EEG changes found in the present investigation, are emphasized during puberty. Some of the found sex differences give further support to this interpretation.

EEG findings in relation to sex

As was discussed in paper I the significantly higher *alpha frequencies* in females in comparison with males points to an earlier maturation in females. This is a pre-pubertal sign, as the mentioned difference is not verified in the post-pubertal period. An indication of an earlier maturation in girls than in boys may also be the higher incidence of *SPR* and the lower incidence of *SIL* in girls during the prepubertal period in corresponding chronological ages. Girls have a more "organized" low frequency activity than boys.

The changed sex distribution with a significantly higher incidence among females than males as regards *SIL* from the age of 14 years indicates an altered homeostasis related to puberty. A similar sex difference was also found in normal adults by Selldén (65).

The cause of the significant sex difference which in this investigation has characterized the *mu rhythm* as a mainly "female trait" and the *anterior 6—7 Hz activity during drowsiness* as a mainly male trait" may be a matter of different maturation of different brain areas for the two sexes. The sex difference, however does not appear in the post pubertal period, which may indicate that the differentiation of maturation concerning these patterns is successively smudged out during the last part of the studied age period.

That female react more to activations such as HV and IPHS than males may correspond to a higher degree of excitability in females, which is also indicated by their higher incidence of *paroxysmal activity*. A sex difference with predominance for adult females to various affects of activation procedures was also reported by Selldén (65). The sex difference in the present investigation as regards paroxysmal activities was most apparent after puberty. This is consistent with the endocrine differences between the sexes. In this context it must be mentioned the significantly higher blood pressure, especially diastolic, in females as compared to males, which in its turn may explain the lower incidence of spontaneous sleep in females, again indicating the female trait of a high level of excitability. That another latent mechanism such as the "adrenalin arousal" may also be a contributary cause has been discussed in paper I.

It can also be mentioned that besides endocrine mechanisms suggested to influence the EEG genetic factors are of some significance. A genetic influence has been proved by several authors especially regarding *paroxysmal activity* and *14-6-PS* (10 11 12, 16 17 54 55 61 64 75). It is possible that the patterns mentioned in the present investigation also have a genetic origin for 14-6-PS this was proved in a part of the present material of normal subjects by Petersén and Akesson (61)

monics and subharmonics to the different flicker frequencies in the adolescent group than among children Photic driving thus can be regarded as a sensitive useful indicator of brain *maturation and probably reflects* the frequency content of the EEG in general

Some EEG variables show primarily an other course with increasing age. *SIL* for in stance, shows a lower percentual incidence in ages up to 6—7 years than in older children This course may to some extent depend on the fact that in the younger children it is difficult to differentiate SIL from the rela tively more prominent *SPR* SPR may con ceal SIL. The incidence of SIL and MIL in the present investigation corresponds fairly closely to what Gibbs and Gibbs (30) have called S—1" or slightly slow waking activity consisting of scattered slow waves with a frequency of 5 to 7 cycles per second in adults (adjusted downward for children) with an admixture of a small amount of slower activity"

The incidence of SIL shows a levelling around 9—13 years of age whereupon it de- clines. The occurrence in the early twenties fairly well corresponds to figures reported in normal adults (27 65 78)

Since the visual estimation of low frequen cy activity is performed in regard to the chronological age the recorded maximal in cidence of SIL at 9—13 years of age does not per se mean that there is an increase in the absolute amount of low frequency activity during the preceeding age period This may mean that the content of low frequency acti vity decreases with increasing age, but at a slower rate before and a faster rate after ages around 9—10 years.

The accuracy of evaluation of the *content* of non rhythmic low frequency activity and its differentiation from the rhythmic one will increase with the frequency analysis (20 52) and the incorporation of modern methods of correlation analysis and use of automatic data processing

As regards *HV* where a maximal incidence of responses is found around 9—11 years of age, the low incidence of responses in children younger than 6 years can at least to some extent be explained by the fact that these children perform a weak and uneven venti lation After the seventh year of life there is a tendency however towards a real increase in incidence of responses up to the mentioned age maximum With increasing age there is a progressively faster decline in incidence of response to HV which is in accordance with a possible maturational process younger subjects react with EEG changes at HV on the whole more than the older ones, and more so as regards posterior and diffuse changes with frequencies within the delta range, while the older children respond with anterior changes.

After showing a slight increase in incidence up to around 7—9 years, the course of the occurrence of *paroxysmal activity* excluding 14-6 PS also shows a successive decrease. The course of the curve in Fig 12 resembles the morbidity curve for maximum penetrance of paroxysmal especially centrencephalic" EEG phenomena shown by Metrakos and Metrakos (54) Bray an Wiser (11) and Doose *et al* (17) This course corresponds to the declining inception of primary (idiopathic) epilepsy The findings in the present investi gation of slower spik and wave complexes in younger individuals changing to spikes and sharp waves of faster frequencies in the older ones further stresses the role of *brain matu-ration* the brain in earlier phases of devel opment shows a tendency to produce slower irregular waves than a more mature brain (Illustrated for example in Fig 6, paper II and Fig 7 paper IV) This was shown by Grossman (32) in kittens of various stages of *maturation* in which seizures were induced electrically or by metrazol

It is important to note that the maturational development of EEG patterns is not always gradual This can be *illustrated by the rhyth-mic 6—7 Hz activity in anterior derivations during drowsiness mu rhythm* and the *an terior delta response to HV* which patterns

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The only patterns still showing an evident "surviving" tendency at the end of the investigated age span are the *rhythmic 6—7 Hz activity in anterior derivations during drowsiness* and *14-6-PS*. As regards 14-6-PS this has also been shown by Gibbs and Gibbs (29).

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It can also be mentioned that besides endocrine mechanisms suggested to influence the EEG, genetic factors are of some significance. A genetic influence has been proved by several authors especially regarding *paroxysmal activity* and *14-6-PS* (10, 11, 12, 16, 17, 54, 55, 61, 64, 75). It is possible that the patterns mentioned in the present investigation also have a genetic origin; for 14-6-PS this was proved in a part of the present material of normal subjects by Petersén and Åkesson (61).

Maturation

The development of many of the described EEG variables in relation to age has shown characteristic courses The *alpha frequency* increases successively during the whole investigated age span The incidence of *high frequency photic driving* also increases gradually with a faster increase around 9—12 years of age — females showing this augmentation somewhat earlier than males Other EEG variables show a course dependent on a successive increase in incidence up to around 10—12 years of age, whereupon a more or less rapid decline occurs, while a few have a successively declining course throughout the age span investigated The mentioned decline is sometimes different with respect to sex e g *SIL or paroxysmal activity* Around puberty thus some intrinsic mechanisms, probably endocrine ones, influence the developmental course of many of the EEG variables studied. The different rates of decline may reflect different rates of maturation between sexes as well as between brain areas This process takes place more rapidly in females than in males, a fact wich is supported by their biological development (73 76)

The finding of an expression of *14-6-PS* in the adolescent group which is much less pronounced than in the child group along with the fact that paroxysmal responses occur sporadically and of an equivocal character in adolescents as compared to children, is another sign of a maturational process.

Findings such as the positive correlation between age and *alpha frequency* as well as age and *photic driving response to 20—24 flashes/sec* found in the post pubertal period did not appear if only adolescents 16—21 years were studied (paper IV) This may be an expression for a tapering off of the maturational process during the last part of the age period investigated which is in accordance with the general conception of the terminal ordinary growth in man (76)

The interrelations between different EEG variables, as shown in Table VI, indicate obvious individual differences in the maturation pattern with a concentration of certain age-dependent factors to some individuals low frequency patterns are positively correlated with each other as well as with paroxysmal phenomena, but negatively correlated to alpha frequency and high frequency photic driving This would indicate a slower maturation in certain individuals.

The obtained EEG findings motivate a longitudinal study in order to further elucidate the brain maturation process especially before during and after puberty where distinct changes of the EEG occur A longitudinal study during the whole period of active growth with follow up would, of cause, be of utmost value. Such a study on the children reported on in this investigation is now in progress.

Normal EEG

The total investigation has been carried out as a transverse examination of the EEG in normal individuals aged 1 through 21 years. The question is, if the different EEG phenomena recorded represent normal EEG findings as they are recorded in normal individuals? The possibility of loopholes" in the selection method must be pointed out. The present material including subjects with certain surprising EEG patterns, according to earlier knowledge is based on criteria of normality which today seem satisfactory Are these EEG findings an expression of the variation of the normal maturation or a sign of some unknown injury of the brain? A follow up study on the children here investigated is in progress and will possibly increase our knowledge in this respect. Before this has been carried out the results are suggested to form a base for definition of a normal — "healthy — EEG

The present investigation has shown the significance of the fact that age and, to a certain degree, also sex must be accorded more attention than hitherto at the judgement of the EEG in children and adolescents.

SUMMARY

Purpose This investigation has been undertaken to achieve an increased knowledge of the EEG characteristics of normal individuals aged 1 through 21 years in relation to age and sex, and to ascertain the normal variation of the EEG thereby obtaining a more solid basis than hitherto for the evaluation of records from children and adolescents with different disease states. The investigation has been carried out as a tranverse study

The *selection* was based on the following criteria of normality: 1 An uneventful prenatal, perinatal, and neonatal period 2. No disorders of consciousness (sporadic syncope, however was accepted) 3 No head injury with cerebral symptoms, 4 No history of central nervous system diseases 5 No obvious somatic disease 6. No convulsions; 7 No family history of convulsive disorders other than those secondary to acquired cerebral damage 8 No paroxysmal headache or abdominal pain 9 No enuresis or encopresis after the fourth birthday 10 No tics, stuttering, pavor nocturnus or excessive nailbiting 11 No obvious mental diseases 12. No conduct disorders 13 No deviation with regard to mental and physical development.

The subjects were collected from well-baby clinics, child-care homes, nursery schools, common schools, trade schools, schools for education of nurses, physiotherapists, and secretaries, as well as military and municipal institutions. The past history of the subjects was controlled three times, and the delivery files were checked. A somatic examination was performed emphasizing neurological *status*.

The total *material* comprises 928 normal subjects — 483 females and 445 males. The corresponding figures for the child group (1—15 years) is 743—389 and 354 and for the adolescent group (16—21 years) 185—94 and 91 The material is described in some social family aspects. In view of the established aim for the investigation the total material can be regarded as composing a unitary defined sample of normal children and adolescents for EEG examination.

Method The EEGs were taken with either a Grass or a Kaiser electroencephalograph, and the 10—20 electrode system of the International Federation was used with bipolar derivations (including 1 montage with a common reference lead) EEG was recorded at rest in all subjects, during hyperventilation in 86 % of them, during *intermittent* photic stimulation in 85 %, and during sleep in 85 %.

Results The amount of *non rhythmic low frequency activity* was estimated at rest, and the records were classified as having "minute" "normal" "slightly increased (SIL) and moderately increased (MIL) amount of low frequency activity always related to age. In the child group the incidence of SIL+MIL was found in 14 % while the figure for the adolescent group was 4 9 %. The incidence of *rhythmic low frequency activity in posterior derivations* — slow posterior rhythm or SPR — was 25% and 0.5%, respectively

Children did *not respond to activation by hyperventilation* in 9.3 %, while the adolescents did not in 19 %. The corresponding figures for *non-response to intermittent photic stimulation* were 6.8% and 4 9%, respectively *Spontaneous sleep* was attained in 31 % in the child group and in 63 % among adolescents.

The incidence of *paroxysmal effects* (psychomotor variant pattern, 6 Hz spike-and-wave phenomenon, and 14 and 6 Hz positive spike phenomenon excluded) in the child group was 15 % and in the adolescent group 4 9 %. The figures for *psychomotor variant pattern* were 0 8 % and 1 1 %, respectively and for *6 Hz spike-and-wave phenomenon* 1 1% and 3.8 %, respectively

14 and 6 Hz positive spike phenomenon occurred among children in 16% and among adolescents in 15 %. This pattern appeared most distinctly in bi temporal derivations. In 96 % of the subjects with this phenomenon it emerged within 5 minutes of light sleep

An EEG with no signs of SIL, MIL or pa

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Findings such as the positive correlation between age and *alpha frequency* as well as age and *photic driving response to 20—24 flashes/sec* found in the post pubertal period did not appear if only adolescents 16—21 years were studied (paper IV) This may be an expression for a tapering off of the maturational process during the last part of the age period investigated which is in accordance with the general conception of the terminal ordinary growth in man (76)

The interrelations between different EEG variables, as shown in Table VI indicate obvious individual differences in the maturation pattern with a concentration of certain age-dependent factors to some individuals low frequency patterns are positively correlated with each other as well as with paroxysmal phenomena, but negatively correlated to alpha frequency and high frequency photic driving This would indicate a slower maturation in certain individuals.

The obtained EEG findings motivate a longitudinal study in order to further elucidate the brain maturation process especially before, during and after puberty where distinct changes of the EEG occur A longitudinal study during the whole period of active growth with follow up would, of cause, be of utmost value. Such a study on the children reported on in this investigation is now in progress

Normal' EEG

The total investigation has been carried out as a transverse examination of the EEG in normal individuals aged 1 through 21 years. *The question is, if the different EEG phenomena* recorded represent normal EEG findings as they are recorded in normal individuals? The possibility of loopholes in the selection method must be pointed out. The present material including subjects with certain surprising EEG patterns, according to earlier knowledge is based on criteria of normality which today seem satisfactory Are these EEG findings an expression of the variation of the normal maturation or a sign of some unknown injury of the brain? A follow up study on the children here investigated is in progress and will possibly increase our knowledge in this respect. Before this has been carried out the results are suggested to form a base for definition of a normal — "healthy — EEG

The present investigation has shown the significance of the fact that age and, to a certain degree, also sex must be accorded more attention than hitherto at the judgement of the EEG in children and adolescents.

SUMMARY

Purpose This investigation has been undertaken to achieve an increased knowledge of the EEG characteristics of normal individuals aged 1 through 21 years in relation to age and sex, and to ascertain the normal variation of the EEG, thereby obtaining a more solid basis than hitherto for the evaluation of records from children and adolescents with different disease states. The investigation has been carried out as a tranverse study

The *selection* was based on the following criteria of normality: 1 An uneventful prenatal, perinatal, and neonatal period 2. No disorders of consciousness (sporadic syncope, however was accepted) 3 No head injury with cerebral symptoms 4 No history of central nervous system diseases 5 No obvious somatic disease 6 No convulsions 7 No family history of convulsive disorders other than those secondary to acquired cerebral damage 8. No paroxysmal headache or abdominal pain 9 No enuresis or encopresis after the fourth birthday 10 No tics, stuttering, pavor nocturnus or excessive nailbiting 11 No obvious mental diseases 12. No conduct disorders 13 No deviation with regard to mental and physical development.

The subjects were collected from well-baby clinics, child-care homes, nursery schools, common schools, trade schools, schools for education of nurses, physiotherapists, and secretaries, as well as military and municipal institutions. The past history of the subjects was controlled three times, and the delivery files were checked. A somatic examination was performed emphasizing neurological status.

The total *material* comprises 928 normal subjects — 483 females and 445 males. The corresponding figures for the *child* group (1—15 years) is 43—389 and 354 and for the adolescent group (16—21 years) 185—94 and 91 The material is described in some social family aspects. In view of the established aim for the investigation the total material can be regarded as composing a unitary defined sample of normal children and adolescents for EEG examination.

Method The EEGs were taken with either a Grass or a Kaiser electroencephalograph, and the 10—20 electrode system of the International Federation was used with bipolar derivations (including 1 montage with a common reference lead) EEG was recorded at rest in all subjects, during hyperventilation in 86 % of them, during intermittent photic stimulation in 85 %, and during sleep in 85 %.

Results The amount of *non-rhythmic low frequency activity* was estimated at rest, and the records were classified as having "minute" "normal" "slightly increased" (SIL) and "moderately increased" (MIL) amount of low frequency activity always related to age. In the child group the incidence of SIL+MIL was found in 14 % while the figure for the adolescent group was 4 9 %. The incidence of *rhythmic low frequency activity in posterior derivations* — slow posterior rhythm or SPR — was 25% and 0.5%, respectively

Children did *not respond to activation by hyperventilation* in 9.3 %, while the adolescents did *not in 19 %*. The corresponding figures for *non-response to intermittent photic stimulation* were 6.8% and 4 9%, respectively *Spontaneous sleep* was attained in 31 % in the child group and in 63 % among adolescents.

The incidence of *paroxysmal effects* (psychomotor variant pattern, 6 Hz spike-and-wave phenomenon, and 14 and 6 Hz positive spike phenomenon excluded) in the child group was 15 % and in the adolescent group 4 9 %. The figures for *psychomotor variant pattern* were 0.8 % and 1 1 %, respectively and for *6 Hz spike-and-wave phenomenon* 1 1% and 3 8 %, respectively

14 and 6 Hz positive spike phenomenon occurred among children in 16% and among adolescents in 15 %. This pattern appeared most distinctly in bi temporal derivations. In 96 % of the subjects with this phenomenon it emerged within 5 minutes of light sleep.

An EEG with no signs of SIL, MIL or pa

roxysmal phenomena both at rest and during activations, i.e. a *totally "normal" EEG* was found in normal children at 68%, the figure for normal adolescents was 77%.

EEG findings in relation to age and sex

Many of the described EEG variables have shown characteristic development in relation to age and sex.

The *alpha frequency* showed a successive slight augmentation with age — the mean value for the child group being 9.3 Hz (S.D. 0.8) and for the adolescent group 10.2 Hz (S.D. 0.9). Females showed a higher alpha frequency throughout.

The content of *low frequency activity* decreased with increasing age — the decrease seeming slower before and faster after ages around 9—10 years. A preponderance for males as regards *SIL* was found up to 8 years of age while the reversed sex incidence was noticed after 14 years of age. The incidence of *SPR* increased from one year of age and reached a maximum at 5—7 years (40—60%) whereupon there was a progressive decline. SPR occurred more often in females than males in the age group 2—8 years.

At *hyperventilation* there was a maximal incidence of responses around 8—10 years of age. The low effect to hyperventilation in children younger than 6—7 years can be explained by the fact that these children perform a weak and uneven ventilation. With increasing age there was a progressively faster decline in incidence of response to hyperventilation.

As regards *intermittent photic stimulation* the decrease in incidence of *low frequency photic driving* and the increase in *high frequency photic driving* showed the same trend throughout the investigated age period. The rate of change, however, increased around 8—12 years of age — females showing this change about 1 year before the males.

The incidence of *paroxysmal activity* increased slightly up to around 7—9 years, whereupon there was a successive decline. Females presented paroxysmal activity more than males after puberty.

Rhythmic 6—7 Hz activity in anterior derivations during drowsiness, mu rhythm and the *anterior delta response to HV* appeared at certain age levels without apparent antecedent growth from slower activity present at earlier ages. The anterior 6—7 Hz rhythm as well as *14-6-PS* were the only patterns with an incidence exceeding 10% at the end of the investigated age span. These patterns as well as mu rhythm showed a maximal incidence in the early teens. The anterior 6—7 Hz activity was characterized as a mainly "male" trait, while the mu rhythm was mainly a "female" trait.

Maturation

It is suggested that the relation of different EEG variables to increasing age is consistent with a common maturation process, which is most evident from the ages around 9 years. Photic driving can be regarded as a sensitive useful indicator of brain maturation and probably reflects the frequency content of the EEG in general. Acceleration of maturation of the brain, as estimated from the EEG changes found in the present investigation, shows the definite influence of puberty on the incidence of the EEG variables studied. The different rates of decline around puberty regarding several EEG variables may reflect different rates of maturation between sexes as well as between brain areas. This process takes place earlier in females than in males, a fact which is supported by their biological development.

In the adolescent group there were fewer differences in regard to sex and no age dependence in comparison with results obtained with children. This may be an expression for a tapering off of the maturational process during the last part of the age period investigated, which is in accordance with the general concept of the terminal ordinary growth in man.

Whether some of the EEG findings observed are expressions of a normal maturation or signs of some unknown brain injury in spite of the strict criteria of normality will be elucidated when the follow-up study of the investigated children has been carried out. It is suggested that the obtained findings will form the base for a definition of a normal — "healthy" — EEG

The present investigation has shown the significance of the fact that age and, to a certain degree, also sex must have primary consideration at the judgement of the EEG in children and adolescents.

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ACTA PÆDIATRICA SCANDINAVICA

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TRANSTHORACIC IMPEDANCE

WITH SPECIAL REFERENCE TO NEWBORN INFANTS AND THE RATIO AIR-TO FLUID IN THE LUNGS

BY TORSTEN OLSSON AND LARS VICTORIN

ALMQVIST & WIKSELL - STOCKHOLM SWEDEN

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BY TORSTEN OLSSON AND LARS VICTORIN

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FROM THE DEPARTMENT OF PEDIATRICS, CHILDREN'S HOSPITAL, UNIVERSITY OF GÖTEBORG, AND THE RESEARCH LABORATORY OF MEDICAL ELECTRONICS, CHALMERS UNIVERSITY OF TECHNOLOGY GÖTEBORG, SWEDEN

Transthoracic Impedance,

with Special Reference to Newborn Infants and the Ratio Air-to-Fluid in the Lungs

BY

TORSTEN OLSSON LARS VICTORIN

In collaboration with
WILLIAM DAILY
INGEMAR KJELLMER

GÖTEBORG 1970

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1970

Preface

The present supplement is a result of joint work of the Department of Pediatrics, Children's Hospital, University of Göteborg, and the Department of Medical Electronics, Chalmers University of Technology, Göteborg. It represents a part of a medical-electronical research project concerning the process of adaptation to extrauterine life and the intensive care of the newly born infant.

A new method for the investigation of the ratio air/fluid in the lungs of newborn infants, transthoracic impedance technique, is described technically and the results obtained from clinical studies are presented.

The investigations were made possible through the generous support, interest and valuable advice received from the heads of our departments, Professor Petter Karlberg, in Pediatrics, and Professor Henry Wallman, in Medical Electronics. Great help with instrumental service, calculations and other necessary work was given by Mr Tage Sundqvist. We also extend our thanks to Mr Bo Justusson for his advice concerning the statistical problems, and to Miss Ulla-Britt Kjell for skilled help with the clinical investigations.

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Expressens prenatalfond

Torsten Olsson   Lars Victorin

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Contents

SECTION 1

SECTION 2

SECTION 3

Main abbreviations used in the text

TTI	Transthoracic impedance
ECI	Infants with early clamping of the umbilical cord
LCI	Infants with late clamping of the umbilical cord
FRC	Functional residual capacity
V_A	Air volume
ΔV	Change of air volume
V_T	Air volume change with a breath tidal volume
V_E	Extracellular fluid volume in the thorax
$\lvert Z_e \rvert$	Magnitude of the impedance at end-expiratory level basic impedance
$\Delta \lvert Z \rvert$	Change of magnitude of impedance
$\lvert Z_T \rvert$	Change of magnitude of impedance with a breath tidal impedance
$\lvert Z_d \rvert$	Difference in magnitude of impedance between points of mid inspiration and mid expiration on air volume curves
a	Inter-electrode distance
C	Compliance of the lungs

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Contents

SECTION 1

SECTION

SECTION 3

Introduction

When a child is born and separated from its mother it is suddenly faced with new demands on its own organ systems. The first and most vital factor is the commencement of gas exchange across the alveolo-capillary membrane in the lungs after air filling and the closely related adaptation of the circulatory system from a foetal to an intermediate and finally adult type of circulation. The adaptation processes in the newborn are very rapid, with time-constants very much shorter than those found in physiological changes in later life.

The physiological processes of the perinatal period have been subjected to thorough investigations in animals, before, during and after birth (2 4 5 18 22 29 32, 34 35 41 53 55 81 87 100). Considerable knowledge has been gained from these investigations with respect to both the uncomplicated course and the pathophysiological development in disturbed neonatal adaptation.

For human beings it is, however obviously difficult to explore the entire perinatal period, and studies are mainly confined to the postnatal period. Respiratory variables, from the very first breath have been thoroughly investigated (1 12 25 27 40 49 57 58 59 61 65 66 71 91 102). Studies on the immediate postnatal circulatory changes generally require the insertion of intravascular catheters and can be technically demanding. The results obtained may be difficult to interpret particularly due to remaining functioning foetal shunts in and outside the heart. The radioisotope methods used in adult medicine which do not require catheters in central vessels, have been rarely utilized in this particular age group (110 111) due to technical difficulties.

Although special techniques have allowed knowledge to be gained about circulatory events in the newborn infant (8, 1 35 48 70 107), "the question of blood volume changes in the lungs at birth remains unresolved (Avery 1968) (13).

Further knowledge about the respiratory and circulatory adaption is essential not only to widen our cognizance of the physiology of extra-uterine adaptation but also to gain further experience from the clinical point of view of pathological conditions in newborn infants.

Findings have been made in autopsies which suggest that nearly all newborn infants show signs of aspiration of amniotic fluid with debris in the airways and large or small atelectasis as a result (8 69).

One of the great problems in neonatology is furthermore the hyaline-membrane-disease which especially strikes premature infants, with a high mortality rate. The patho-physiology of this disease, which affects both the respiratory and circulatory variables of the lungs is known to a certain extent (13 27 94 101 109). Hypoperfusion of the pulmonary bed was found in in vivo investigations (26 27 109) as well as considerable congestion with blood and lymph in autopsies (36 54 68 76 89). Many questions however remain to be elucidated in order to deal with the disease adequately.

It is thus obvious that for the study of variations in air volume fluid and blood volume and kinetics in the lungs during physiologic and patho-physiologic adaptation to extra-uterine life, it would be of value to have an external technique which is easy to apply without side-effects and imposing no burden on the newborn infant during the vulnerable period following delivery.

The number of techniques available for studying the newborn infant is restricted for reasons arising from the difficult conditions prevailing in the immediate neonatal period. Large differences between the adaptation patterns of the

The results from the different studies are integrated in a general discussion in Section 3 in which the above parts are referred to with their respective Roman numerals.

The prenatal lung

In the uterus the future airways the trachea, the bronchi and the alveoli, are expanded and filled with fluid. The total lung volume is considered to conform with that found after neonatal adaptation (4 5 71). The fluid is produced over the epithelium in the airways and in many respects resembles plasma (1 93 103). Differences found in the Donnan equilibrium for certain ions between this so called bronchial fluid and plasma however suggest that an acti e secretory process is involved in the production of the fluid (103). The protein content of the bronchial fluid is further more low 20–30 mg per 100 ml, and the acidity high pH 6.40 as compared with the plasma (1)

The pressure in the pulmonary artery is comparatively h gh about 60 mm Hg but due to the high pulmonary vascular resistance the pulmonary blood flow is low constituting approximately one tenth of the right heart out put The major amount of blood is shunted directly from the right to the left side of the circulation through the foramen ovale and the ductus arteriosus, by passing the lungs. The pulmonary blood flow is under neuro-humoral control and can be affected by pharmacological means (20 34) With increased oxygen tension and or reduced carbon dioxide tension in the blood, the pulmonary blood flow increases Wide spontaneous ariations in the flow can, however be found without noticeable variation in blood gases (35)

Investigations on lambs before and after deli ery have proved that the lymph production in the lung prenatally is more than double that of an animal a few days old—this in spite of the low blood flow It ha been suggested that this dif ference in lymphatic flow pre and post-natally depends on differences in capillary permeability rather than on capillary pressure (103).

Adaptive changes at b rth

Air-fill ng of the lungs

Breathing is initiated through a multitude of exogenous and endogenous stimuli to the respiratory centre The first breath is taken with considerable variation in intra thoracic pressure During inspiration the negative pressure ranges between 20 and 70 cm H_2O while the first expiration is often active and expelled against the partially closed glottis, resulting in a positive pressure wave (56, 58) The total variation in pressure during the first breath may thus be about 100 cm H_2O

Already with the first breath a functional residual capacity (FRC) is formed. The air filling of th lungs then increases rapidly so that at 15 minutes of age the FRC has reached about 3/4 of its value after one week (65) By one to three hours the FRC is relatively stable and after the first 24 hours of life there is little further increase up to the age of one week (25 49 59 65 66)

Studies of the mechanical properties of the lungs have shown that there is initially a low pulmonary compliance This expression of the distensibility of the lungs, i e air volume change per unit pressure change is usually stated in ml/cm H_2O An increase has been found during the first week of lif and particularly the first day from 2 to about 4 ml/cm H_2O (25 37 66) This increase especially applies to infants with initially low compliance (37) and who are subjected to late clamping of the um bilical cord (80) In the interpretation of these findings both differences in blood volume and air content of the lungs have to be considered, as FRC is lower in late-clamped infants than in early-clamped infants during th first hours of life

The bronchial fluid

In order to establish extra-uterine gas ex change over the lung epithelium it is essential that the bronchial fluid can be rapidly replaced by air In vaginal deliveries the compression of the thorax causes a certain evacuation of the

individual patients together with the small time-constant characterizing physiological development in the neonatal period provide evident reasons to prefer methods that allow on line continuous recording to be performed

The introduction of practical instrumentation for impedance measurement of simultaneously occurring changes in intrapulmonary fluid and air volume would represent a significant advance with regard to the recording of these variables and suggests one possible means by which such changes might be monitored and perhaps quantified The method has the very great asset of fundamental simplicity in so far as the infant is concerned This is a problem of no small concern in view of the fact that particularly for diseased infants there is considerable risk attached to repeated handling of the infant for diagnostic or therapeutic purposes.

Since the baby can remain connected to the instrument during routine nursery care the impedance technique has the great advantage of allowing continuous studies to be performed. The response is furthermore fast enough to record even the most rapid physiological events

In the neonatal period measurement of transthoracic impedance (TTI) is used under different circumstances to record variations with respiration and has proved to be of clinical value in apnoea monitoring (31 83 84 90) The possibility of obtaining information concerning the behaviour of fluid and air volumes in the lungs with TTI in combination with an uncorrelated method for air volume determination, has not been investigated earlier The prime importance of these questions concerning the newborn infant has prompted studies to be performed on animals and on infants during the first day of life constituting the basis for the present report

Aims of investigation

The aims of the investigation have been

- to evaluate the various portions of the TTI which arise from the electrical characteristics of the thoracic structures and the geometrical shape of the thorax
- to evaluate the electrical basis for the interpretation of TTI in terms of intrathoracic volumes,
- to achieve safe practical reliable and easily handled equipment suitable for application to the newborn infant and satisfying the requirement of permitting continuous, on line measurements,
- to evaluate the practical possibility of studying the ratio air/fluid in the lungs
- to study the dynamic correlation of air and blood in the lungs of the newborn infant during respiration,
- to study possible changes in the ratio air/fluid in the lungs during the first few hours of life
- to study the effects of early and late clamping of the umbilical cord on the ratio air/fluid during the first day of life and
- to create a physical model for the static and dynamic ratio air/fluid in the lungs based on physiological evidences to be applied to our experimental and clinical results

A review of relevant data concerning perinatal pulmonary and circulatory physiology and adaptation will be presented, followed by a discussion of electrical fundamentals and the measuring of physiologic events by electrical impedance

The studies are presented in Section 2 in the following parts

Transthoracic impedance

I Theoretical considerations and technical approach

II Experimental evaluation of the method in the cat

III Methodological studies in newborn infants.

IV Studies of the infant during the first two hours of life

V Effects of early and late clamping of the umbilical cord with special reference to the ratio air to-blood during respiration.

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fluid which is replaced by air due to the elastic recoil of the thorax after partus (60) The residual amount of bronchial fluid that has not been drained through the upper airways is re sorbed into interstitial space blood and lymph vessels That this takes place very quickly is *inter alia* proved by the rapid air filling of the lungs. The greater part of the bronchial fluid is in the lamb drained within the first few minutes (103)

The relative importance of drainage via blood or lymph has been discussed Immediately fol lowing the onset of respiration using inter mittent positive-pressure respiration in lambs, Boston *et al* found a considerable increase in the lymph flow from the lungs (18) This increase during the first two hours of life corresponded to 1/3 of the fluid and the entire amount of protein lost from the lungs during this time A histological examination revealed a simul taneous "expansion of the lymphatic space so prominent that the pulmonary arteries appeared to be suspended in distensible tunnels" as pointed out by Aherne and Dawkins (5) With the increase in flow of lymph out of the lungs from about 0 6 to 2 1 g per kg body weight and hour a reduced protein content of the lymph occurs at the same time from approximately 2 1 to 1 4 g per 100 ml, to rise again as the flow decreases after some hours (18 53 103)

No direct information is available concerning the uptake of bronchial fluid into the capillaries lining the alveoli In view of the abundance of these capillaries the increase in blood flow through the lungs a favourable osmotic dif ference between blood and bronchial fluid and finally free permeability to water through the alveolo-capillary membrane (103) it appears reasonable to take also this route into considera tion for the drainage of the bronchial fluid out of the lungs

The neonatal circulation

The postnatal air filling of the lungs initiates an instantaneous decrease in the resistance of the pulmonary vessels The pressure in the pulmonary artery drops partly due to the air fluid interface formed in the alveoli and the resulting forces of surface tension. The changes in blood gases with a decrease in P_{CO} and increase in P_{O} having a direct dilating effect mainly on the arterioles is also of great im- portance for the reduction of the vascular resistance (22 29 34) The three factors gas expansion fall in P_{CO} and rise in P_{O} have about equal importance for the increase in pulmonary blood flow (34)

The difference in pressure between the pul monary artery and the aorta which previously was positive with a flow from right to left in the ductus arteriosus, will progressively become negative causing the pulmonary blood flow and probably also the pulmonary blood volume to increase (35 41 81 107) The ductus arteriosus through which the blood is conveyed from left to right will mainly owing to the increased oxygen content start to decrease in diameter during the first hours after birth to close com pletely as a rule in the first week of life (2 28 33 48 86 87 95 100 109)

The functional importance of the right to-left shunt through the foramen ovale diminishes already within the first few minutes after birth mainly due to an increase in pulmonary blood flow and hence also in left atrial pressure (2 28 90 100 109)

Both the respiratory and the circulatory adaptation is affected by the magnitude of the placental transfusion. Late clamping of the um bilical cord as compared to early clamping means that after 15 minutes of life the blood volume is about 30 per cent greater a difference which decreases during the first 24 hours but does not entirely disappear (79 100) During the first few hours the late-clamped infants have a higher pressure both in the left and the right atrium as well as in the pulmonary artery A smaller difference in pressure be- tween the aorta and the pulmonary artery with less left-to-right shunting enables the ductus arteriosus to remain open longer as a high O_2 tension in the blood is the main stimulus for its constriction (9) The neo-natal situation concerning the pulmonary circulation is complex

and the above described circumstances are not stationary Small changes in blood gases or pressure in the thorax, such as those created during breathing, may alter the pattern, particularly as long as the ductus arteriosus remains anatomically open.

Great variations of blood shunting are found, both within groups of newborns with an un eventful perinatal course and within a single case on repeated determinations. In general a right to-left shunt is detectable during the first hour after birth while a left-to-right shunt persists, according to Arcilla *et al.* (10) to disappear some time during the second half of the first day of life. A longer persistence of the left-to-right shunt was noted in late clamped infants. Gessner *et al.* (48), who did not especially in estigate the effect of placental transfusion, found a right to-left shunt for about one hour and a left to-right shunt for seldom longer than three hours

In conclusion, the individual differences are pronounced and the shunting of blood is influenced by a number of factors, such as quiet breathing crying and cardiac cycle especially during the first hours of life (2).

Lung water

The water content of the lungs as determined in animals decreases after birth by 10 to 25 per cent of the total pulmonary weight This change i most pronounced from 30 minutes to tw hours of ge, during which time 3/4 of the total reduction has taken place (5 81). During the same time an approximately twofold increase of the pulmonary blood volume was noted in these animals (81) No specific detailed study on the fluid volume hange during the first 30 minutes has been reported.

Electrical fundamentals

When a voltage is applied across two points on a olume conductor a current will flow through the conductor The relation between oltage and current is expressed by Ohm s law

$$E = ZI \qquad (1)$$

where E is the voltage I the current and Z a factor called impedance. In this equation E and I are functions of frequency expressed by their complex representations. It follows that the impedance also is represented by a complex function. Separated in real and imaginary parts Z can be written as

$$Z = R + jX, \qquad (2)$$

where R is the resistance X is the reactance and the j is the well-known symbol for $\sqrt{-1}$ For zero frequency when X is zero Eq 1 can be written in the well known form

$$E = RI \qquad (3)$$

Impedance can also be expressed as $Z = |Z| \text{ ang } \varphi$ in terms of its magnitude $|Z|$ and phase angle φ defined by

$$|Z| = \sqrt{R^2 + X^2} \qquad (4)$$

and

$$\varphi = \arctan (X/R) \qquad (5)$$

It should be noted that for small phase angles $|Z|$ is almost equal to R. When $\varphi = 10°$ for instance, that is when X/R is 0 18 the magnitude of the impedance $|Z|$ is 1.02 R.

In a conductor with uniform current density the impedance is determined from a material constant, the characteristic impedance z, and the dimensions of the conductor The resistive part of the characteristic impedance is called resistivity and commonly denoted ρ. The impedances of homogeneous volume conductors are directly proportional to the characteristic impedance if they are of the same size and shape. The impedance of volume conductors of the same material but different shape is not evaluated in a simple manner except for a very few body shapes.

Impedance measurements of physiological events

Measuring the impedance of biological material is of interest for various reasons. One reason is to determine the specific impedance of tissues to be used for the calculation of the

fluid, which is replaced by air due to the elastic recoil of the thorax after partus (60) The residual amount of bronchial fluid that has not been drained through the upper airways is re sorbed into interstitial space blood and lymph vessels. That this takes place very quickly is *inter alia* proved by the rapid air filling of the lungs The greater part of the bronchial fluid is, in the lamb drained within the first few minutes (103)

The relative importance of drainage via blood or lymph has been discussed. Immediately fol lowing the onset of respiration using inter mittent positive-pressure respiration in lambs Boston *et al* found a considerable increase in the lymph flow from the lungs (18) This increase during the first two hours of life corresponded to 1/3 of the fluid and the entire amount of protein lost from the lungs during this time A histological examination revealed a simul taneous "expansion of the lymphatic space so prominent that the pulmonary arteries appeared to be suspended in distensible tunnels as pointed out by Aherne and Dawkins (5) With the increase in flow of lymph out of the lungs from about 0 6 to 2 1 g per kg body weight and hour a reduced protein content of the lymph occurs at the same time from approximately 2 1 to 1 4 g per 100 ml to rise again as the flow decreases after some hours (18 53 103)

No direct information is available concerning the uptake of bronchial fluid into the capillaries lining the alveoli. In view of the abundance of these capillaries the increase in blood flow through the lungs a favourable osmotic dif ference between blood and bronchial fluid and finally free permeability to water through the alveolo-capillary membrane (103) it appears reasonable to take also this route into considera tion for the drainage of the bronchial fluid out of the lungs

The neonatal circulation

The postnatal air filling of the lungs initiates an instantaneous decrease in the resistance of the pulmonary vessels The pressure in the pulmonary artery drops partly due to the air fluid interface formed in the alveoli and the resulting forces of surface tension. The changes in blood gases with a decrease in P_{CO} and increase in P_{O} having a direct dilating effect mainly on the arterioles is also of great im portance for the reduction of the vascular resistance (22 29 34) The three factors, gas expansion fall in P_{CO} and rise in P_{O} have about equal importance for the increase in pulmonary blood flow (34)

The difference in pressure between the pul monary artery and the aorta which previously was positive with a flow from right to left in the ductus arteriosus will progressively become negative causing the pulmonary blood flow and probably also the pulmonary blood volume to increase (35 41 81 107) The ductus arteriosus, through which the blood is conveyed from left to right will mainly owing to the increased oxygen content start to decrease in diameter during the first hours after birth to close com pletely as a rule in the first week of life (9 28 33 48 86 87 95 100 109)

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from the current was measured by the two other lectrodes. This voltage was transformed to an impedance value The instruments used in Parts II and V measured the magnitude of the impedance |Z| while the instruments used in Parts III and IV measured the resistive part R of the impedance. The instruments provided recordings of the basic impedance $|Z_0|$ as well as impedance variations $\Delta|Z|$ from the basic impedance.

Air-volume change during respiration, in Parts III and V were recorded with a reverse plethysmograph consisting of a glass bottle with a volume of 65 litres. The reverse plethysmograph used in Part II had a volume of five litres and was included in a balanced closed system

Lung blood volume of cats in Part II was measured, after intravenous injection of human serum albumine tagged with ^{131}I by a scin tillation detector via a gamma-spectrometer to a ratemeter

Oesophageal pressure (Part V) was recorded by means of an open polyethylene, saline filled catheter in the caudal third of the oesophagus, connected to a pressure transducer

distribution of bioelectric signals such as the ECG EMG and EEG A review of the results obtained for different tissues is presented by Geddes and Baker (45)

Another reason has been to use the impedance of different body segments as an index for various physiological events. The use of impedance technique to record peripheral volume pulses was described by Mann in 1937 (73) Other investigators soon used the same general method and a number of papers appeared dealing with the subject (10 77) In 1932 Atzler and Lehmann (11) reported impedance variations synchronous to the heart activity when the thorax was employed as part of the dielectric of a capacitor At present the analyses of impedance variations of the thorax arising from cardiac activity are concentrated on finding an indirect method of measuring stroke volume in *human subjects* (63 67)

Most investigations applied to the thorax, however have had the object of correlating *impedance variations* with *respiration*. Early reports in which variations related to respiration are described are those of Atzler and Lehmann 1932 (11) and Fenning 1936 (43) Strong correlation between impedance change and breath volume has been demonstrated by many workers (7 16 50 62 84)

Two different techniques are used to measure the impedance In one method two electrodes are used to inject current as well as to measure voltage while in the other technique an extra pair of electrodes is used for the voltage measurement The tetrapolar technique permits the user to exclude the impedance of the injection electrodes and the volume with high current density close to these electrodes.

The *frequencies* used *fall between some* hundred Hz (62) and more than 100 MHz (11) The most commonly used frequencies are between 30 and 200 kHz mainly because in this range the polarization effect of the electrodes is small and the leakage currents in the bridge can be kept at reasonably low values. These frequencies are also to be preferred for reasons of safety (47)

The *quantity measured* is in most cases the magnitude of the impedance or the resistive part of the impedance although most authors mention impedance only A detailed *survey of* the various instrument systems used for impedance measurement on body segments has been given by Pacela (82) who also provides a discussion of the different impedance parameters.

A survey of most physiological events measured by impedance is made by Geddes and Baker (46)

The impedance technique has not escaped criticism The most far reaching critics have been Hill *et al* (51) who concluded that "electrical impedance plethysmography as it is currently used and interpreted appears to be in error In many points their scepticism is justified but there can be no doubt that their conclusion is *exaggerated*

Material

In order to verify the basic concepts concerning current distribution at the electrodes and in the thorax measurements were performed on normal adult males as well as on newborn infants To test the agreement between theory and practice of transthoracic impedance studies were also performed on five anaesthetized full *grown cats*

The studies on newborn infants reported were all carried out on infants with uneventful perinatal course born between 1965 and 1970 at University Department of Obstetrics and Gynecology Sahlgren Hospital and East Hospital Göteborg All longitudinal studies were performed on full term infants with the exception of the control group in Part IV The infants were randomly selected mainly from the neonatal wards supervised by Department of Pediatrics Children s Hospital University of Göteborg

Methods

Transthoracic impedance was measured by a four-electrode instrument supplying a 0.2 mA peak to-peak current of *50 kHz through the* thorax via two electrodes The voltage arising

from the current was measured by the two other electrodes. This voltage was transformed to an impedance value. The instruments used in Parts II and V measured the magnitude of the impedance |Z| while the instruments used in Parts III and IV measured the resistive part R of the impedance. The instruments provided recordings of the basic impedance $|Z_0|$ as well as impedance variations $\Delta|Z|$ from the basic impedance.

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From the Research Laboratory of Medical Electronics, Chalmers University of Technology and the Department of Pediatrics, Children's Hospital, University of Göteborg Sweden.

Transthoracic Impedance
I Theoretical Considerations and Technical Approach

by TORSTEN OLSSON WILLIAM DAILY[1] and LARS VICTORIN

Transthoracic impedance (TTI) has frequently been used as an indirect measure of dynamic respiratory volumes. Impedance technique in the clinic and in physiological research has great instrumental possibilities for qualitative recordings. The theoretical background, however has not been sufficiently penetrated and the use of different instrumentation approaches has led to discrepancies in the interpretation of impedance variations. The following is an attempt t use electrical fundament ls in conjunction with an engineering approach to establish a theoretical and physical model by means of which static as well as dynamic TTI measurements can be i terpreted. Some important instrumentation problems will also be analyzed.

Numerous ttempt have been made to describe TTI variations analytically and empirically as functions of variations in air volume or blood olume within the thorax Frequently however too simple models have been employed or the understanding of basic electrical phenomena has been insuff cient Much criticism ha therefore been voiced against the concept of impedance technique

Current distribution within the thorax

In order to underst nd the origin of the impedance variations that can be detected during measurement of TTI it is imperative to study the lectrical field distribution within the thorax. It is therefore of importance to define the structures through which the current flows. For volume conductors of simple geometry and homogeneous electrical properties the impedance between two points can be determined analytically The thorax, with its unspecified shape and inhomogeneous electrical properties, escapes any attempt at such an analytical description. It is possible, however that with the aid of numerical approximation techniques an estimation of the field could be achieved on the basis of a model of the thorax. This method has been considered impractical due to the extreme difficulties involved in obtaining a mapping of the electrical structures of the thorax. Moreover it is doubtful if it is at all possible to take into account the influence of the major physiological modifications and variations taking place. Consequently we have instead chosen to work with somewhat simpler models and make comparisons with results of in situ measurements.

If the thorax is represented by a cylinder into which current is injected between two points on the mantle, the surface field can be computed or it can be measured in a model. Two extremes have been investigated. In the first case the cylinder is totally filled with a homogeneous electrolyte in the second case the only conductive material is that of a thin layer at the mantle of the cylinder If the current injection is assumed to take place between two points of diametrically opposite locations at the same elevation, the potentials shown in Fig 1 are obtained. In this figure the mid point of the line (on the surface) joining the two injection lectrodes is chosen as the reference point. The

[1] Recipient Ettinger Foundation Fellowship in Pediatrics, Stanford University School of Medicine Palo Alto, California.

Fou -electrode technique

The impedance measured between two skin electrodes is composed of the contact impedance of the metal-electrolyte junction, the impedance from paste to skin and the tissue impedance, which is essentially determined by the electrical field in the neighbourhood of the electrodes

When there is a need for measuring the basic impedance which predominantly reflects the situation in the lungs, and/or for measuring impedance variations without interference from variations in electrode impedance and electrical behaviour of the tissues at the electrodes it is necessary that the measurement be constrained to comprise only part of the electrical field This is made possible by the introduction of another pair of electrodes, the measuring electrodes.

The choice of location of the measuring elec trodes must be the result of a compromise If they are placed close to each other the im pedance is determined by a minor portion of the total electric field causing the static and dy namic levels to be low Th s presents a problem in the design of the measuring instrument If, on the other hand the measuring electrodes are placed close to the injection electrodes, a greater part f the field determines the impedance but there will also be part which will be emphasized, of higher current density A schematic drawing of a sagittal section of the thorax with applied electrodes i shown in Fig —

Th thorac mpeda ce

As mentioned above it is difficult to calculat the lectric field in the thorax and hence to calculat the mpedance Accurat impedance mea urement are ho ever not t be con sidered the principal purpose of the TTI tech nique the nterest is instead directed towards the determination of *variations* in air fluid and other olumes of the thorax. An nalysis of how such variations affect the impedance is therefore of considerable value

The most commonly used frequencies for TTI measurement fall bet een 20 kHz and 100

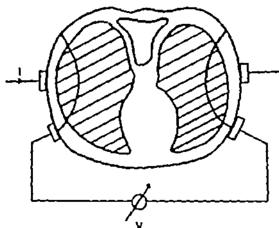


Fig. — Schematic drawing of section of thorax with electrodes pplied for impedance measurement by four electrodes Approximat equipotential lines through measuring electrodes re shown.

kHz. Apart from the resistive component the impedance of biological materials at these fre quencies also shows a reactive component, which comes from the capacitance of the cell membranes. For most tissues including those of the thorax this reactive part is small in the frequency band concerned (10) It is therefore justified to assume in a theoretical analysis of the variations of the TTI that the impedance is purely resistive

For a homogeneous medium the resistance R can be written as

$$R = \rho K \qquad (I\ 1)$$

where ρ is the resistivity of the medium and K i a factor depending upon the shape of the field. Regarding a fixed portion of the lung it is evident that the resistivity varies during breath ing because an increase in air volume must be compensated by a decrease in conducting vol ume thus resulting in an increase of the total resistivity If the total volume is homogeneous and the electric field constant, then resistance variations could be derived from variations in resistivity

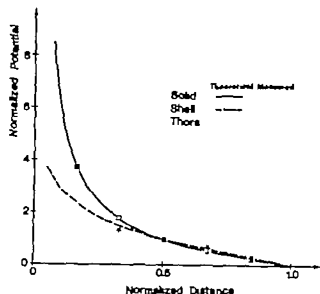


Fig 1 Potential distribution along a quarter of the circumference of a circular section with diametrically placed point electrodes. The values are normalized with respect to the midpoint value. Theoretical values are shown as curves and measured values are marked Thorax values are means from measurements on three adult males and three newborns.

potential differences along the line have been normalized with respect to the value at a point located half way between the reference point and the injection electrode

Theoretical values are easily obtained for the symmetry plane by conformal mapping of a half plane on a circle Thus the potential on the surface of a solid cylinder with the diameter a is proportional to $1/(a \tan \varphi)$ where φ is the midpoint angle The corresponding value for a cylindrical shell is $\ln (1/\tan \frac{1}{2}\varphi)/a$

Measurements have been carried out on models as well as on adults and newborns The electrodes have been applied around the front of the thorax at the mammillary level and measurements made along the line connecting the two electrodes The measured values have been plotted together with the theoretical values (Fig 1) The resulting diagram demonstrates that the actual potential distribution measured on the thorax closely resembles the two distributions obtained by calculations and measurements on a cylinder filled with a conductive medium

The above discussion of the thoracic field pattern can of course not be extrapolated to comprise microstructures in which the current paths around alveoli and through cells are to be studied.

Two-electrode technique

If impedance measurements on the thorax are carried out by means of two electrodes of negligible contact impedances the measured impedance will particularly reflect the situation in those parts of the thorax having the highest current density Regardless of the magnitude of the resistivity the immediate surroundings of the electrodes will have a dominating influence on the total impedance This fact is also evident from Fig 1 In order to avoid influences from this effect which is particularly unfavourable when deeper layers are to be measured it is necessary to create stable conditions around the electrodes This can be achieved in different ways e.g by making the electrodes physically large or by using active electronics to drive guard rings around the electrodes (2) It is also of importance to avoid placement of the electrodes immediately over areas of high resistivity like fat and bone The importance of maintaining stable conditions at the injection electrodes is even more obvious when considering the properties of the practical electrode A metal-electrolyte junction has in itself a relatively high impedance to which has to be added the transfer impedance of the junction between the paste and the low conductive parts of the skin. It is necessary to achieve an approximately uniform current distribution over the whole area through the paste and into the skin This can be implemented by placing the metal-electrolyte junction at some distance from the skin. The paste has rather high conductivity and thus forms a suitable basis for the current to penetrate the upper layer of the skin. Immediately after the application of the electrodes the conduction through the epidermis is unsatisfactory but gradually the paste will find its way through and improve current flow (12)

Four-electrode technique

The impedance measured between two skin electrodes is composed of the contact impedance of the metal-electrolyte junction, the impedance from paste to skin, and the tissue impedance which is essentially determined by the electrical field in the neighbourhood of the electrodes.

When there is a need for measuring the basic impedance which predominantly reflects the situation in the lungs, and/or for measuring impedance variations without interference from variations in electrode impedance and electrical behaviour of the tissues at the electrodes, it is necessary that the measurement be constrained to comprise only part of the electrical field. This is made possible by the introduction of another pair of electrodes, the measuring electrodes.

The choice of location of the measuring electrodes must be the result of a compromise. If they are placed close to each other the impedance is determined by a minor portion of the total electric field, causing the static and dynamic levels to be low. This presents a problem in the design of the measuring instrument. If on the other hand the measuring electrodes are placed close to the injection electrodes a greater part of the field determines the impedance but there will also be parts, which will be emphasized of higher current density. A schematic drawing of a sagittal section of the thorax with applied electrodes is shown in Fig

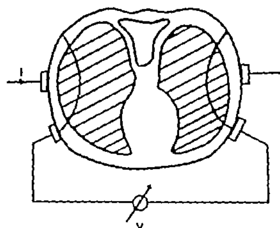


Fig. 2. Schematic drawing of section of thorax with electrodes applied for impedance measurement by four electrodes. Approximate equipotential lines through measuring electrodes re shown.

The thoracic impedance

As mentioned above it is difficult to calculate the electric field in the thorax and hence to calculate the impedance. Accurate impedance measurements are however not to be considered the principal purpose of the TTI technique: the interest is instead directed towards the determination of *variations* in air, fluid and other volumes of the thorax. An analysis of how such variations affect the impedance is therefore of considerable value.

The most commonly used frequencies for TTI measurement fall between 30 kHz and 200 kHz. Apart from the resistive component the impedance of biological materials at these frequencies also shows a reactive component, which comes from the capacitance of the cell membranes. For most tissues, including those of the thorax, this reactive part is small in the frequency band concerned (10). It is therefore justified to assume in a theoretical analysis of the variations of the TTI that the impedance is purely resistive.

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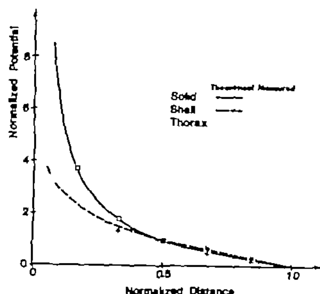


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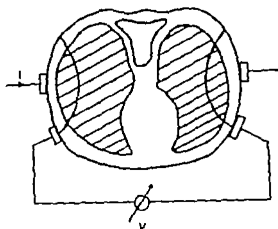


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The impedance and its fluctuations as measured with the two-electrode technique reflect to only a minor extent the conditions within the lungs whereas changes in the conditions close to the electrodes affect the field heavily thereby causing irrelevant impedance variations.

It is possible with the four-electrode technique to choose a section with a more uniform current density which means that small geometrical deviations will affect the impedance to a minor extent only According to Eq I 1 it is thus possible in the case of small geometrical variations in the thorax (normal breathing) to assume K constant and hence to attribute impedance variations to variations in the resistivity

The resistivity of a compound medium consisting of a substance of resistivity ρ_2 in which are disseminated small spheres of resistivity ρ_1 the ratio of the volume of all small spheres to that of the whole being P is according to Maxwell (0) expressed as

$$\rho = \frac{2\rho_1+\rho_2+P(\rho_1-\rho_2)}{2\rho_1+\rho_2-2P(\rho_1-\rho_2)}\rho_2 \qquad (I.2)$$

If we restrict ourselves to the case of nonconducting spheres the expression is simplified to

$$\rho = \frac{2+P}{2-2P}\rho_2, \qquad (I.3)$$

which can be extended to other bodies than spheres via

$$\rho = 1+\left(1+\frac{1}{x}\right)\frac{V_1}{V_2}\ \rho_1 \qquad (I\ 4)$$

In this latter expression V_1 and V_2 denote the volumes of the nonconducting substance and of the remaining volume of resistivity ρ_2 and x is a factor depending on the shape and orientation of the nonconducting bodies (3 11) The relations are restricted to suspensions of low density and homogeneous distribution

A general extention of these equations to a structure as inhomogeneous as the thorax would be erroneous There is however sufficient basis to hypothesize that Eq I 4 provides an approximate expression for the resistivity of the thorax in terms of conducting and nonconducting volumes.

In the following examination of the contributions from the various variables the air is considered nonconducting and the tissue is assumed to be homogeneous with the resistivity ρ_2. The shape-dependent factor x cannot be determined analytically but some values obtained from the original equations are helpful in the estimation of its influence for nonconducting spheres x=2 for cylinders perpendicular to the current pathways x=1 and for cylinders parallel to the pathways x=∞.

The factor $1+(1/x)$ in Eq I 4 thus varies between one and two In large parts of the lungs the current will flow in parallel with the airways due to the structural properties. In comparison with other assumptions it is reasonable to assume x to be large This results in a simple expression for the resistivity of the thorax

$$\rho = \left(1+\frac{V_1}{V_{2}}\right)\rho_2 \qquad (I.5)$$

The volume V_1 mainly consists of the air volume in the lungs V_A and V_{2} is the somewhat reduced conducting volume of mean resistivity ρ_2. The volume V_{2} is very heterogeneous but represents in the first approximation the extra cellular fluid in the thorax This approximation is justifiable for frequencies below at least 1 kHz. It is true that the intracellular fluid is of relatively high conductivity but in the low frequency band the cell membranes act as insulators (0)

In the determination of the resistivity of the conducting volume at higher frequencies it is important to take into account that the current also passes through the cells The relation Eq I.2 used above can also be applied to the problem of finding the resistivity of this tissue where the cells are assumed to be surrounded by a conductive medium The expression is however more complex as the interior of a cell shows high conductivity and the cell membrane has the character of a capacitance. The concept of resistivity is thus modified to that of charac-

impedance which also covers the reactive component. A presentation of the relations realized for the case of variable frequency is found in Cole and Curtis (1). An equivalent network can be constructed based on elements consisting of a resistance in parallel with the combination of a resistance and a capacitance in series (Fig 3). Such an element represents a cell with the surrounding extracellular fluid.

If all the elements were identical, the calculation of a resultant expression would be straightforward. In practice, this is unfortunately not the case and it is necessary to carry out measurements. Such measurements can however not be restricted exclusively to lung tissue. It is difficult to exclude the air from the measurement volume and the characteristics of the structure are dependent on the volume present.

The frequency dependence of the characteristic impedance is the same for lung tissue with and without air, provided the frequency is low enough not to allow any appreciable current to flow through the capacitances of the alveoli and the airways.

Measurements of the characteristic impedance of segments of the thorax have been carried out on adults at frequencies between 1 kHz and 600 kHz, as seen in Fig 4. In the measurements, the current was injected with the electrodes around the neck and the abdomen, and the measurements taken between two electrodes with approximately 10 cm vertical separation, the lower electrode being at about the level of the 6th intercostal space. The instrumentation is identical to the impedance-measuring device to be described below, except that the reactive impedance component also could be measured. The magnitude of the characteristic impedance was normalized with reference to the value measured at 50 kHz (because the results are only intended to give an idea of the frequency dependence). A comparison between this result and the impedance of the circuit of Fig. 3 shows obvious similarities, and it is easily understood that a suitable combination of series or parallel circuits with appropriate component values can give a good match with the results of the measurements.

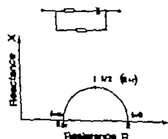


Fig. 3. Schematic equivalent circuit of a cell surrounded by extracellular fluid, and corresponding impedance locus.

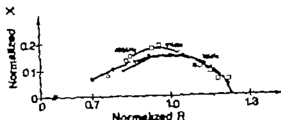


Fig. 4. Impedance locus of a thoracic segment as measured on three subjects. Values are normalized with respect to measured resistive parts at 50 kHz. The figure also corresponds to normalized characteristic impedance locus.

At the frequency of interest, 50 kHz, the magnitude of the characteristic impedance has decreased to approximately 80 per cent of the low frequency value (Fig 4). At low frequencies an expression similar to Eq I:4 can be used for the resistivity of the lung tissue if the air is excluded,

$$\rho_1 = \left(1 + \frac{V_1}{V_E\left(1+\frac{1}{y}\right)}\right)\rho_E \qquad \text{(I:6)}$$

in which V_E denotes the extracellular fluid volume with resistivity ρ_E, V_1 the cell volume and y a shape-dependent factor. If the phase shift is neglected, the decrease in value with increased frequency can be interpreted as a

The impedance and its fluctuations as measured with the two-electrode technique reflect to only a minor extent the conditions within the lungs, whereas changes in the conditions close to the electrodes affect the field heavily thereby causing irrelevant impedance variations.

It is possible with the four-electrode technique to choose a section with a more uniform current density which means that small geometrical deviations will affect the impedance to a minor extent only According to Eq I 1 it is thus possible in the case of small geometrical variations in the thorax (normal breathing) to assume K constant and hence to attribute impedance variations to variations in the resistivity

The resistivity of a compound medium consisting of a substance of resistivity ρ_2 in which are disseminated small spheres of resistivity ρ_1 *the ratio of the volume of all small spheres to* that of the whole being P is according to Maxwell (6) expressed as

$$\rho = \frac{2\rho_1+\rho_2+P(\rho_1-\rho_2)}{2\rho_1+\rho_2-2P(\rho_1-\rho_2)}\rho_2 \qquad (I.2)$$

If we restrict ourselves *to the case of noncon*ducting spheres the expression is simplified to

$$\rho = \frac{2+P}{2-2P}\rho_2 \qquad (I.3)$$

which can be extended to other bodies than spheres via

$$\rho = 1+\left(1+\frac{1}{x}\right)\frac{V_1}{V_2}\,\rho_2 \qquad (I.4)$$

In this latter expression V_1 and V_2 denote the volumes of the nonconducting substance and of the remaining volume of resistivity ρ_2, and x is a *factor depending on the shape and orientation* of the nonconducting bodies (3 11) The relations are restricted to suspensions of low *density and* homogeneous distribution

A general extention of these equations to a structure as inhomogeneous as the thorax would be erroneous There is however sufficient basis to hypothesize that Eq I 4 provides an approximate expression for the resistivity of the thorax in terms of conducting *and nonconducting vol*umes.

In the *following* examination of the contributions from the various variables, the air is considered nonconducting and the tissue is assumed to be homogeneous with the resistivity ρ_T. The shape-dependent factor x cannot be determined analytically but some values obtained from the original equations are helpful in the estimation of its influence for non conducting spheres x=2 for cylinders perpendicular to the current pathways x=1 and for cylinders parallel to the pathways x=∞

The factor 1+(1/x) in Eq I 4 thus varies between one and two In large parts of the lungs the current will *flow* in parallel with the airways due to *the* structural properties. In comparison with other assumptions it is reasonable to assume x to be large This results in a *simple expression for the resistivity of the* thorax

$$\rho = \left(1+\frac{V_1}{V_{zz}}\right)\rho_T \qquad (I.5)$$

The volume V_1 mainly consists of the air volume in the lungs V_A and V_{zz} is the somewhat reduced conducting volume of mean resistivity ρ_T. The volume V_{zz} is very heterogeneous, but represents in the first approximation the extracellular fluid in the thorax. This approximation is justifiable for frequencies below at least 1 kHz It is true that the intracellular fluid is of relatively high conductivity but in the *low* frequency band the cell membranes act as insulators (9)

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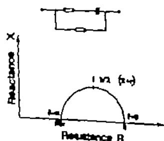


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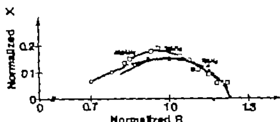


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in which V_E denotes the extracellular fluid volume with resistivity ρ_E, V_I the cell volume and γ a shape-dependent factor. If the phase shift is neglected, the decrease in value with increased frequency can be interpreted as a

transport of volume from V_I to V_E or a decrease in the reducing effect of the factor $1+(1/y)$ We write approximately

$$\rho_I = \left(1 + \frac{V_I}{V_E}\right)\rho_E \qquad (I\ 7)$$

which together with Eq I 4 and $V_I = V_A$ yields

$$\rho = \left(1 + \frac{V_A}{(V_E+V_I)\Big/\left(1+\frac{1}{x}\right)}\right)\left(1+\frac{V_I}{V_E}\right)\rho_E \qquad (I\ 8)$$

or

$$\rho = \left(1 + \frac{V_A+V_I\Big/\left(1+\frac{1}{x}\right)}{V_E\Big/\left(1+\frac{1}{x}\right)}\right)\rho_E \qquad (I\ 9)$$

which can be approximated by

$$\rho = \left(1 + \frac{V_A}{V_E}\right)\rho_E \qquad (I\ 10)$$

The volume dependence of the impedance variations

If we continue to neglect the phase shift the impedance can be referred to as a resistance Considering the relation $R = \rho k$ and assuming that the field pattern is stationary we can determine variations in resistance as functions of variations in volume If V_A and V_E are independent the complete differential of ρ is

$$\Delta\rho = \frac{\partial\rho}{\partial V_A}\Delta V_A + \frac{\partial\rho}{\partial V_E}\Delta V_E \qquad (I\ 11)$$

which applied to Eq I 10 yields

$$\Delta\rho = \left(\frac{1}{V_E}\Delta V_A - \frac{V_A}{V_E^2}\Delta V_E\right)\rho_E = \frac{\Delta R}{k} \qquad (I\ 12)$$

and relative variations in impedance can be written as

$$\frac{\Delta R}{R} = \frac{V_A}{V_A+V_E}\left(\frac{\Delta V_A}{V_A} - \frac{\Delta V_E}{V_E}\right) \qquad (I\ 13)$$

The relative volume variations are proportional to relative impedance variations

The assumption that the volumes are independent causes this equation to be useless for an estimation of the impedance variation induced by an air volume variation. The information on the variation in conductive volume caused by the air volume variation is lacking *We have not studied this relationship analytically* having instead developed a simple model based on fundamental physical laws and physiological variables *On the basis of this model* and information regarding the resultant variations in volume the impedance variations can be determined qualitatively and relatively For measured impedance values $\Delta|Z|/|Z_0|$ are in the analyses considered equal to $\Delta R/R$

A model of the lungs

If the impedance is measured on a simple *model consisting of nonconductive identical* spheres packed as close to each other as possible surrounded by a conducting material and kept in the same container *Fig 5 (1-2)* the impedance value is independent of the radius of the spheres The same result is yielded by Eq I 13 due to the fact that the relative volume variations are equal but of opposite signs The case of different sphere sizes can be considered a linear scale change preserving the ratio of the volumes *Such a situation is of course not* confined to the case of well packed spheres but holds for all structures as long as volume changes take place without changes in shape The model of the densely packed spheres which represent the alveoli *is too simple for a good* representation of the lungs but it shows one phenomenon of importance in the discussion of the lung model to follow an increase in the volume of the spheres causes an increase in *the volume between the spheres This is always* true for structures of elastic material in which the minute volumes are in contact or connected to each other at discrete points

We are of the opinion that parts of the lungs operate in accordance with this model The practical implication of the model is that parts

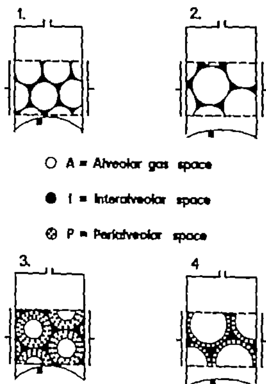


Fig. 5. Physical lung model with
1–2 small amount of fluid,
3–4 larger amount of fluid

of the lungs increase their content of conductive material (such as blood) when the air volume in these areas increases, independently of whether the increase in volume takes place with positive-pressure respiration or with spontaneous breathing. The conductive material can be supplied from different areas. If the material is supplied from areas not applicable to the model but in which the current of the impedance measurement flows, the change in V within the field will be zero and the volume increase causes an increase in impedance. If the material on the other hand is supplied from areas through which no current passes the increase in impedance is more or less cancelled in the model of well packed spheres. In order to demonstrate these situations we extend the model as shown in Fig 5 (3–4). Here the sphere (the alveoli and the airways) is surrounded by a shell consisting of conductive medium (perialveolar volume) and we still have a volume (inter alveolar volume) which changes in proportion to the sphere volume. The perialveolar volume comprises all volume independent of the shape-dependent fraction, including the volume of e.g. major vessels. Measurements on this model would show an increase in impedance proportional to the volume until the whole perialveolar volume were transferred to interalveolar volume. An additional increase in volume would not cause any further impedance changes. The model would now be the one of Fig 5 (1–2). In practice there is a continuous transition between the models with and without a perialveolar volume because of different compliance of different structures. In terms of V_E this can be interpreted as a tendency to display a large relative impedance change for a certain change in air volume when V_E is large whereas the impedance change in case of a smaller V_E is smaller for the same change in air volume.

The model without a perialveolar volume requires that conductive material (blood) can be taken from outside the field, which in the practical case means from outside the thorax. We therefore modify the model by encapsulating the structure in a cylinder with a piston. The cylinder has two outlets, one combining all the spheres with the external air and the other connecting the volume in between the spheres to a reservoir with a fluid. In spontaneous breathing, as the piston makes the total volume increase the pressure evoked will enhance the volumes V_A and V_E, but the distribution will be determined by the compliance of different systems to some extent interdependent because of the shape-dependent fraction. The communication from V_A and V_E with areas outside the thorax is an important feature of the model. For example the high intrathoracic pressures in the case of the closed epiglottis subsequent to the first inspiration (5) can be given a logical explanation if this mechanism is kept in mind because in this way the thorax can be depleted of fluid volume.

When it is of interest to utilize the model for studying rapid dynamic changes, it is im

transport of volume from V_1 to V_E or a decrease in the reducing effect of the factor $1+(1/y)$. We write approximately

$$\rho_1 = \left(1 + \frac{V_1}{V_E}\right)\rho_E \qquad (I\ 7)$$

which together with Eq I 4 and $V_1 = V_A$ yields

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If we continue to neglect the phase shift the impedance can be referred to as a resistance. Considering the relation $R = \rho K$ and assuming that the field pattern is stationary we can determine variations in resistance as functions of variations in volume. If V_A and V_E are independent the complete differential of ρ is

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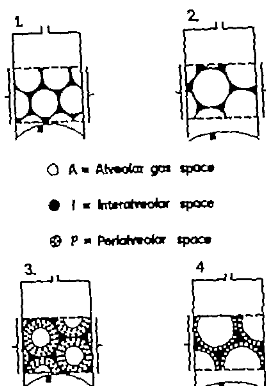


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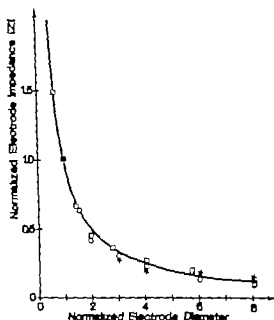


Fig. 6. Normalized magnitude of inter-electrode impedance as function of electrode diameter. A theoretical curve is shown. Experimental values are derived from two different male subjects and from Pasquali (□) (●)

from the injection location to ensure that electrode variations have negligible influence on the measurement of the impedance. The four electrode method can be compared to the two-electrode method with two electrodes of the same shape as the equipotential surfaces on which the measurement electrodes are applied. These equipotential surfaces are clearly dependent on the shape of the field around the injection electrodes but the influence diminishes rapidly as the distance is increased, see Fig. 1

Simultaneously with the impedance measurements for different electrode sizes, a study was also carried out on the impedance between two symmetrically located measurement electrodes at distance equal to one half of the total between the injection electrodes. The magnitude of the impedance shows no dependence on the size of the injection electrode. The mean value, normalized to the same impedance as was done before is 0.01 with a standard deviation of 8 x 10

In order to obtain as stationary conditions as possible during the measurements we have designed combination electrodes as seen in Fig 7. The electrodes consist of one injection electrode and one measuring electrode in the same housing, thus keeping the critical distance between injection electrode and measurement electrode constant. We have chosen this distance to be two cm. These electrodes have an equivalent size corresponding to the electrode diameter with normalized value four in Fig. 6.

The remaining geometrical variable of Eq I 14 is the interelectrod distance. In case of transthoracic measurement on newborns this value is about 10 cm affecting the impedance magnitude to about 20 per cent. If the cross-section of the thorax is more elliptical, with the interelectrode distance equal to the main axis, the distance will be increasingly critical. In the extreme case in which the current density is almost constant throughout most of the volume the impedance will be proportional to the distance. The question whether the distance should be taken into consideration in the practical case depends on where the electrodes are applied on the thorax, and the question has to be left open until practical measurements have been carried out.

Instrumentation

The measurement bridges utilized in the present investigation are of our own design. They are based on the half bridge principle with constant-current drive. One version has been

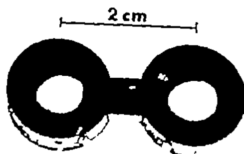


Fig. 7 Dual floating electrode.

perative that the flow resistance of the two systems be taken into account One problem is the difficulty of predicting the influence of the *active pressure regulating system* on the blood side No analysis of this phenomenon has been undertaken

Another case of importance in the analysis of impedance changes during a breath should however be emphasized. During active inspiration the air and blood systems are subject to the same pressure whereas under passive expiration the elasticity of the individual systems provide driving forces. This may cause the impedance and air variations to differ between expiration and inspiration if the time constants of the systems are different

Electrodes and electrode placement

It is of importance in the verification of our hypotheses to be able to register transthoracic impedance statically and dynamically The essential demand on an instrument for this purpose is that it permit the measurement of impedance without having the results distorted by the contact impedances A measuring bridge of the four-electrode type is then required if the electrodes are to be of practical size As mentioned above the impedance of a volume conductor is chiefly determined by the size and shape of the electrodes. As a relevant example of the influence of the electrodes the magnitude of the impedance of a sphere can be mentioned We neglect the portion of the impedance that can be attributed to the metal-electrolyte junction. If the electrodes are of negligible size in comparison to the diameter of the sphere have the shape of calottes bulging into the sphere and if they constitute the equipotential surfaces of the analytical solution for two diametrically opposite point electrodes then the expression for the resistance R takes the simple form

$$R = \frac{\rho}{2\pi}\left(\frac{1}{r_1} + \frac{1}{r_2} - \frac{2}{a}\right) \qquad \text{(I 14)}$$

This expression has three terms two of which depend on the radii r_1 r_2 of the electrodes and the third on the diameter a of the sphere In the case of small electrodes the latter part will make an insignificant contribution. If the electrodes are segments of the surface of the sphere a similar expression will be obtained but involving factors determined by an infinite sum of coefficients of Legendre polynomials of first order (13) The resistance calculations can also be extended to other shapes of the volume but as there is no basic difference between the methods of solution in the various cases, most of the resistance will still be dependent on the size and shape of the electrodes. Eq I 14 provides an adequate approximation for all bodies of dimensions much larger than those of the electrodes if spherical symmetry is assumed in the vicinity of the electrodes If surface electrodes are used on the thorax for current injection an analytical study is no longer possible due to the varying resistivities in the vicinity of the electrode A change in resistivity such as that occurring subsequently to the application of an electrode as the paste penetrates the otherwise low-conductive upper layers of the skin, can be considered to be an equivalent change of the electrode surface It is easily understood that such changes can cause significant impedance variations.

In order to investigate the validity of our assumption regarding spherical symmetry in the case of electrodes applied on the thorax we have measured the magnitude of the impedance between two circular electrodes diametrically applied on the thorax The electrode diameter was varied between 6 and 80 mm The results were normalized with reference to the value for diameter 10 mm and are presented in Fig 6 The figure also contains the theoretical curve. Values published by Pasquali normalized in the same way are also included (8)

The accordance indicated in the figure between measurement results and theoretical values shows that the assumptions of spherical symmetry around the electrodes is justifiable

The method usually employed in electrical measurements for avoiding the large influence of the field at the injection electrodes is to measure only that part of the field far enough

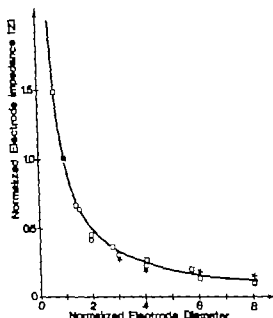


Fig 6. Normalized magnitude of inter-electrode impedance as function of electrode diameter. A theoretical curve is shown. Experimental values are derived from two different male subjects and from Pasquali (□) (8)

from the injection location to ensure that electrode variations have negligible influence on the measurement of the impedance. The four electrode method can be compared to the two-electrode method with two electrodes of the same shape as the equipotential surfaces on which the measurement electrodes are applied. These equipotential surfaces are clearly dependent on the shape of the field around the injection electrodes but the influence diminishes rapidly as the distance is increased, see Fig. 1

Simultaneously with the impedance measurements for different electrode sizes, a study was also carried out on the impedance between two symmetrically located measurement electrodes at distance equal to one half of the total between the injection electrodes. The magnitude of the impedance shows no dependence on the size of the injection electrode. The mean value, normalized to the same impedance as was done above is 0.012, with a standard deviation of 6 × 10

In order to obtain as stationary conditions as possible during the measurements we have designed combination electrodes as seen in Fig 7. The electrodes consist of one injection electrode and one measuring electrode in the same housing thus keeping the critical distance between injection electrode and measurement electrode constant. We have chosen this distance to be two cm. These electrodes have an equivalent size corresponding to the electrode diameter with normalized value four in Fig 6.

The remaining geometrical variable of Eq I 14 is the interelectrode distance. In case of transthoracic measurement on newborns this value is about 10 cm affecting the impedance magnitude to about 20 per cent. If the cross-section of the thorax is more elliptical, with the interelectrode distance equal to the main axis the distance will be increasingly critical. In the extreme case in which the current density is almost constant throughout most of the volume the impedance will be proportional to the distance. The question whether the distance should be taken into consideration in the practical case depends on where the electrodes are applied on the thorax, and the question has to be left open until practical measurements have been carried out.

Instrumentation

The measurement bridges utilized in the present investigation are of our own design. They are based on the half bridge principle with constant-current drive. One version has been

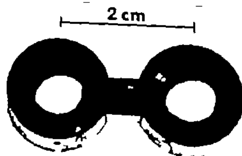


Fig 7 Dual floating electrode

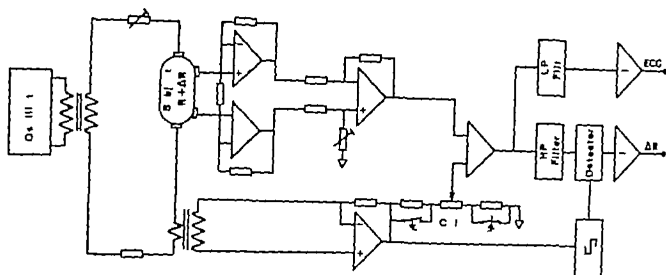


Fig 8. Block diagram of the impedance instrument

described in detail (7) whereas the most recent version permitting continuous registration and built with employment of integrated circuits will be described below The principle of the instrument is shown in the block diagram of Fig 8 In addition to the blocks in the figure the instrument also includes heart and respiration frequency meters the operation of which is not to be discussed here

The oscillator is a 50 kHz Clapp oscillator with a differential power stage driving a symmetrical transformer The bridge part consists of the secondary winding of the oscillator transformer two series resistances a reference resistance and electrode connections The transformer winding and the two series resistances form the current generator which essentially has the source resistance of the two series resistances The current is adjusted to 0.2 mA peak to-peak This current is well under the level of tissue stimulation or fibrillation (4) but is large enough not to give noise problems A fixed rather than adjustable reference resistance has been chosen in the bridge this reduces stray capacitances In an instrument where only the resistance or the magnitude of the impedance is of interest such an arrangement provides the great advantage that the leakage current can be kept reasonably small

The most difficult practical problem arising in the design of a bridge for measurement of impedance on large unscreened volume conductors from 20 kHz upwards is in the fact the control of the leakage currents. The leakage currents have two main negative effects With the electrodes applied the bridge in balance and the measurement object fixed with regard to the environment leakage currents through the stray capacitances can cause various currents to flow through the measurement object and the reference resistance causing errors in the calibration of the bridge In view of the fact that TTI measurements are not precision measurements these errors are negligible as long as the leakage currents are small A more serious situation occurs when the object is in motion or when leakage currents are changed for other reasons e g because the object is touched The change in leakage current will then appear as a change in impedance and this change may well be of the same order as the impedance variations of interest for the measurement It is of particular importance to keep these errors small when the static impedance is registered over long periods of time and in the case of patient monitoring A simple analysis of the bridge with possible leakage current paths may indicate where improvements of the bridge can be undertaken in order to make the bridge insensitive to such external disturbances.

In the present analysis the diagram shown in Fig 9 is used. A simplification has been made

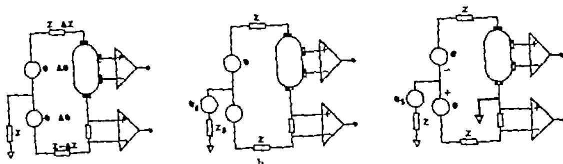


Fig. 9 Schematic diagram of the constant current bridge used for leakage current analyses. For details, see text.

in that all stray impedances to ground, both discrete and continuous have been combined into one impedance Z_i connected to the merging point of the two voltage generators, which physically consist of the secondary windings of the transformer The two voltage generators and source impedances are assumed to be unsym metrical, with values Δe and $\pm \Delta Z$ respectively Disregarding second and higher-order effects, we can modify the bridge as shown in Fig. 9*b* A voltage generator e is now introduced in series with the ground impedance Z_i and is specified by the quantities Δe and ΔZ as

$$e = \Delta e + (\Delta Z/Z)e \qquad (I\ 16)$$

If an object is connected according to Fig 9c and worst-case grounding is performed, i.e. in such way that the ground currents through bject impedance and reference resistance are equal but opposit the maximal acceptable un balances for certain tolerable influence on the measurement can be specified. Let a one-ohm deviation in the magnitude of the measured impedance be acceptable This deviation cor responds to 0.5 per ce t change in the current through the reference resistor if worst-case grounding is performed and the measurement object is 100 ohm resistor This means that the in phase portion of the ground current can be at most 2 microamperes peak to-peak in our bridge resulting in an unbalance voltage of 0.3 to olt peak to-peak when Z_i varies between zero and 10^4 ohm resistively Such an unbalance correspond t a 0.5 t 3.3 per cent unbalance in the voltage or in the source resistances.

We can draw the conclusion that a higher insulation impedance permits a higher unbalance in the bridge. However the bridge voltage with reference to the ground potential constitutes a common mode voltage from the point of view of the measurement amplifier and the reference amplifier Heavier demands will be put on these instruments. A maximal deviation in measured impedance value of one ohm when the worst point is grounded according to the above discussion corresponds to a common-mode rejection ratio of 62 to 80 dB when Z is varied between zero and 10^4 ohm.

A more complicated ground situation will undoubtedly appear in the practical applications, and f rthermore the stray impedances encountered n practice will be predominantly capacitive making it vital to consider the in fluence of the reactive component Also the sensitivity to ground currents will be affected by the method of detecting the impedance variations. Practical experience indicates, how ever that a minimization of the ground current effects according to the above discussion results in a recording that is sufficiently disturbance-free. Summing up, it is vital to decrease the unbalance voltage of the bridge with reference to ground, to increase the insulation impedance to ground and to increase the common mode rejection ratio of the measurement and refer ence amplifiers.

Various instruments have been used in our experiments. All of them however are based on the current-driven half bridge with a 50 kHz 0.2 mA peak to-peak current. The source

impedance is essentially resistive with a magnitude of more than 600 kohm. The instrument used in some investigations measured the magnitude of the impedance and the variations of the magnitude (7) In most of the investigations use was made of a phase-sensitive detector to determine the impedance with a reference signal in phase with the current through the reference resistor The impedance values measured by these instruments are to be considered as *the resistive part of the impedance* The difference between the magnitude of the impedance and the resistive part is about two per cent as the phase angle of the transthoracic impedance is 5 to 10 degrees. The use of phase sensitive detectors is advantageous in that it is easy to construct a linear phase-sensitive detector with a larger dynamic range than an ordinary envelope detector The linearity is essential as it is necessary to avoid intermodulation noise from e g ECG signals that are amplified in the same amplifier as the 50 kHz *signal* *The phase-sensitive* detector has furthermore lower inherent noise than the envelope detector normally used

The measuring amplifier shown in the block diagram (Fig 8) is the one of those tried giving the best overall result Another amplifier with field-effect transistors used as followers at the input has also been used but tedious matching was necessary to achieve the same common mode rejection ratio (>80 dB) With the amplifier shown and with use of two per cent resistors in the feed back network only one *adjustment is used* to achieve this common mode rejection ratio at 50 kHz The common mode dynamic range is also larger

Instead of the reference resistor shown in the earlier schematic drawings of the bridge part the block diagram shows a current transformer connected to a current amplifier A direct connected differential amplifier is easier to design but higher insulation impedance is obtained with the transformer In both cases the amplifier *outputs are set to* the reference value of 100 ohm resistive.

The current-source transformer is constructed carefully employing bifilar winding technique, in order to obtain maximal symmetry Remaining unbalance is removed by trimming one of the source resistors so that the current-fed connectors assume zero potential with respect to ground.

The switch resistor arrangement around the balance potentiometer is made to give a constant one-ohm calibration signal over the entire range 0–100 ohm

The phase-sensitive detector is a field-effect transistor connected as a shunt gate and gated by a square wave obtained from the reference signal The filter amplifier has a bandwidth of 200 Hz.

Two types of active control of the leakage currents have been tried as seen in Fig 10. One involves driving a *center tap of the source* transformer from the output of an inverting amplifier with the common mode voltage of the me-

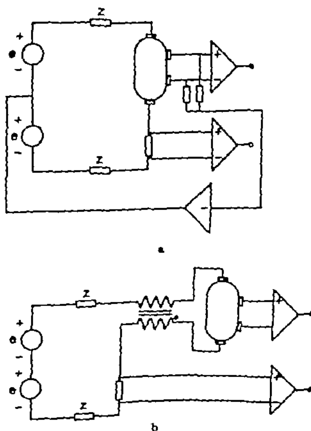


Fig 10 Two different ways t mi imize leakage currents.

a Common mode feedback.

b. Current suct oning by an i terphase transformer

asuring-amplifier fed to the inverting amplifier setting up a feedback loop that reduces the common-mode voltage Another way is to con nect a bifilar wound transformer to the current feeding branches of the half bridge This will strive to keep the current leaving one output equal to the current entering the other These two extra options, separately or together yielded no measurable improvement when applied to a properly-adjusted circuit. When applied to a circuit in which no adjustment of leakage currents has been performed the effect of active control can, however be striking We had no reason to include these options, as the instruments were to be used under continuous engineering control In instruments designed for routine clinical use the options do add an extra feature of reliability to the already easily handled equipment

Specification of the instruments

Bridge current 0.2 mA p. t. p. 50 kHz.

Reference resistor 100 ± 1 ohm.

Linearity of balance potentiometers 0.5 per cent.

One-ohm calibration 1 ohm ± 5 per cent over the entire range 0–100 ohm

For trimming a 50 ohm resistor was used as a model The instruments were adjusted so that deviation in the output was less than the corresponding value of half an ohm,

ii resistor of 10 kohm was inserted as a contact impedance at one or both injection electrodes,

i resistor of 1 kohm was inserted to give unbalance in the source impedance of the measuring amplifier or

ii the worst point according to Fig 8c was grounded.

Summary

For the analysis of measured values of TTI the thorax can be regarded as a practically homogeneous volume conductor A theoretical model is developed by which TTI can be evaluated in terms of volumes of the thorax The instrumentation is described, and an analysis is made of the influence of leakage currents

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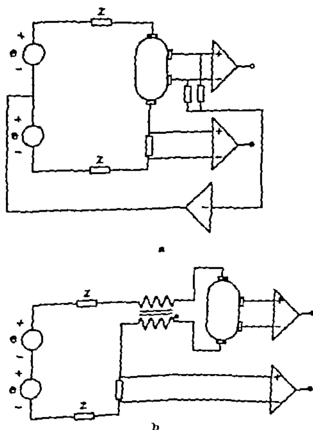


Fig. 10. Two different ways to minimize leakage currents.
a Common mode feedback.
b Current sectioning by an interphase transformer.

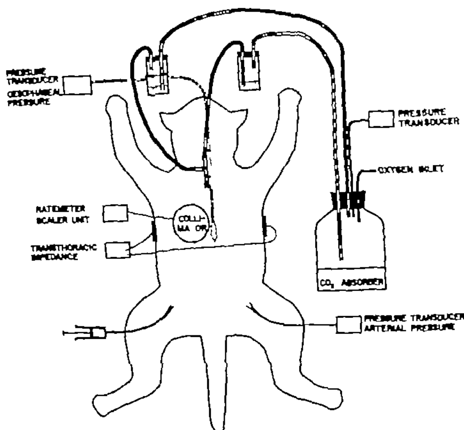


Fig. 2. Schematic representation of the experimental set-up. See text for details.

The cats lay in the supine position with the electrodes placed bilaterally in the mid-axillary line as far cranially as possible under the fore-legs. Electrodes used were of a floating type consisting of silver discs with a diameter of 10 mm and filled with hypertonic electrode paste (Cambridge Elec Co N Y) Interelectrode distance was kept constant by mechanical fixation of the electrodes.

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Signals for blood pressure ventilation, lung radioactivity and transthoracic impedance were displayed on a Grass Polygraph, model 7 A schematic representation of the experimental set up i given in Fig. 2.

F ve experiment were performed. In the first two changes in TTI with a varying blood volume were studied. In the other three (III–V) changes of the pulmonary blood volume were also monitored with the isotope technique described.

Results

Variations of the lung blood volume The lung blood volume was varied by changing the total blood volume of the cat. This was done by stepwise withdrawal of 5 to 50 ml of blood with a syringe and later retransfusion.

In every instance a reduction of the blood volume was accompanied by a raised impedance while an increased blood volume was linked to a decreased impedance.

In the three cats in which variations of the pulmonary blood volume were studied with the isotope technique totally 41 sequences of with drawal-retransfusion were performed. A repre-

the lung. This resistivity ρ_L is a function of the resistivity of the conducting parts of the lung ρ_E and the relation between volumes of conducting parts, mainly blood V_E and non-conducting parts mainly air V_A (5). The expression for the resulting resistivity is thus

$$\rho_L = \rho_E(V_A + V_E)/V_E$$

and the resistance can be written as

$$R = K_1(V_E + V_A)/V_E \qquad (II:2)$$

where K_1 is a constant derived from K and ρ_E.

A small relative variation in V_E and V_A creates a variation in R according to the expression

$$\frac{\Delta R}{R} = \frac{V_A}{V_A + V_E}\left(\frac{\Delta V_A}{V_A} - \frac{\Delta V_E}{V_E}\right) \qquad (II.3)$$

The purpose of the study is to assess the validity of the assumptions outlined above and to test the quantitative relationship given in the formula.

When interpreting measured impedance values |Z| they are considered equal to the resistance R. The error hereby induced is less than two per cent in absolute value.

Methods

Full grown cats weighing 2.8–3.8 kg were used as experimental animals. They were all anaesthetized with chloralose 60 mg/kg after ether induction and given heparin 1000 IU/kg intravenously.

Ventilation. Ventilation was recorded with a modification of the reverse plethysmograph principle (2). A T cannula was inserted in the trachea and connected to a five-litre glass bottle via simple valves consisting of water locks making the respiratory air circulate through the system. The bottle contained a CO_2 absorber (soda lime) and was fitted to a tube for oxygen supply and to a pressure transducer (Statham P23 BC) for measuring pressure fluctuations within the system. Because of the CO_2-absorption a steady fall of the pressure in the system occurred that was compensated by a corresponding flow of oxygen into the bottle.

The volume-recording system was calibrated by sudden injection and withdrawal of 10 ml of air. The signal from the pressure transducer gave a direct recording of both tidal volume and of change of the end-expiratory level.

The end-expiratory pressure could be varied by the expiratory valve. It was usually kept at a level of one cm H_2O but at intervals was abruptly raised five cm H_2O.

Lung blood volume. Twenty minutes before an experiment 4–5 mC of human serum albumin tagged with ^{131}I (AB Atomenergi, Studsvik, Sweden) was given intravenously. The activity was recorded with a scintillation detector via a gammaspectrometer to a ratemeter (Packard Electronics 1½″ × 2″ thallium activated sodium crystal Tricarb spectrometer and model 310A ratemeter). The detector with a collimator of honeycomb shape was placed over the lower right portion of the thorax. It registered the emission from a cone with its base being 25 mm in diameter at the thoracic surface and a top angle measuring 30° extending downwards into the lower lobe of the right lung. The positioning of the collimator could be done in such a way that no part of the heart was included in the cone (see Discussion). Dose figures used for calculations represent a counting time of one minute. Recorded intensity was achieved from a ratemeter with a time constant from 0.5 to 3 sec.

The blood volume of the cat was varied with a 50 ml syringe into which blood was drawn from the right femoral artery and from which it was retransfused to the cat through the right femoral vein. Before the start of an experiment 25 ml of a dextran solution (Rheomacrodex®) was given intravenously and allowed to equilibrate for 30 minutes so that the blood volume of the animal was varied around the initial level.

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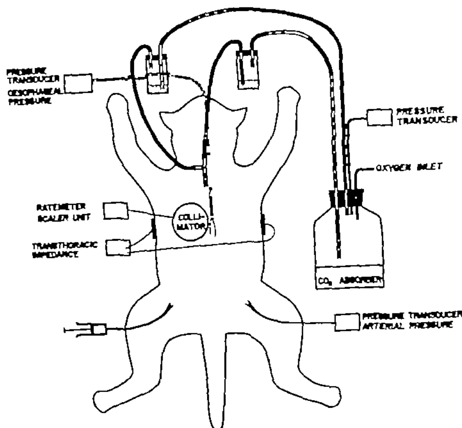


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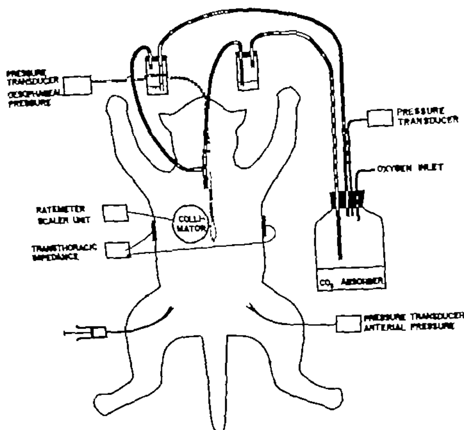


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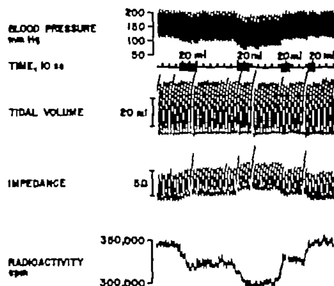


Fig 3. Stepwise withdrawal and retransfusion of *0 ml of blood Concomitant variations are noted in arterial blood pressure impedance and radioactivity while end expiratory level and tidal volume remain virtually unchanged (Cat N V)

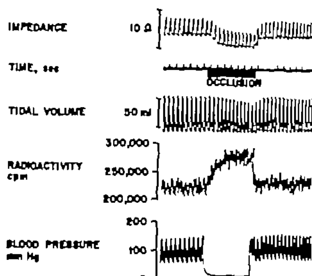


Fig 4 Sudden occlusion of bdominal aorta and commo carotid arteries induces an increase f radioactivity together with a lecreased impedance while FRC is virtually unchanged. Blood pressure as measured distal t the occluded orta, falls t zero (C t No. IV)

sentative example is shown in Fig 3 In every case a change of the cat s total blood volume was concomitant with a change in the same direction of the lung blood volume In the whole series of experiments the average decrease of total blood volume obtained in one step was 30±14 ml or 12 0 per cent if the total blood volume is assumed to be 250 ml This created an average reduction of 11 6±0.. per cent of the lung blood volume

The lung blood volume was also varied through a redistribution of the total blood volume within the cat This was achieved by a sudden occlusion of several large arteries the abdominal aorta and the common carotid arteries The procedure resulted in an abrupt elevation of the lung blood volume and was performed in one cat altogether four times Fig 4 gives an example In each instance the transthoracic impedance fell in the same way as when the lung blood volume was increased via a retransfusion

The relation between changes in relative impedance and relative pulmonary blood volume in the instances when the blood volume was varied with the techniques mentioned are illustrated in Fig 5

A negative linear correlation is obvious fro the figure and is significant indeed as judged from the r values (cat III 0 99 cat IV 0 91 cat V 0 98) i e an increasing pulmonary blood volume is concomitant with a falling transthoracic impedance

Blood was also redistributed from the systemic into the pulmonary circulation by pharmacological means Periods of constant intravenous infusion of large amounts of norepinephrine (10–100 μg/min) resulted in an elevation of the lung blood volume accompanied by a fall in transthoracic impedance (Fig 6) in the same way as when the lung blood volume was elevated by other means. Infusions of norepinephrine were administered altogether five times in two cats with qualitatively identical results.

Variations of the end-expiratory pressure Stepwise changes of the end-expiratory pressure produced abrupt changes of the volume of air contained in the lungs Increasing the end expiratory pressure by five cm H_2O raised the end-expiratory level (FRC) by an average of 16 9±6 7 ml in 13 experiments on three cats. The result from one of these is shown in Fig 7 An increase of the FRC was closely followed by an increase of the TTI When the end-expiratory

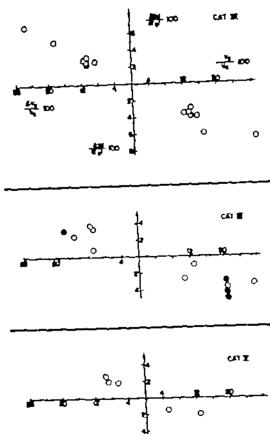


Fig 8. Correlation between change in relative pulmonary blood volume and relative impedance. Included are all instances where concomitant change in air volume was small (< 5 ml). Empty circles = pulmonary blood alone varied through withdrawal or retransfusion. Crossed circles = pulmonary blood volume varied through occlusion and release of great arteries.

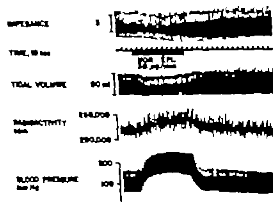


Fig 6. During constant norepinephrine infusion the radioactivity increases with concomitant fall of impedance (Cat No. IV)

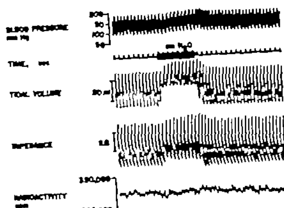


Fig 7. During sudden increase of airway expiratory pressure end-expiratory level (FRC) increases immediately as does end-expiratory impedance level $|Z_0|$. No measurable change is noted in the radioactivity (Cat No. V)

pressure was reduced again, both the FRC and the TTI returned to the initial level.

Variations of the end-expiratory pressure sometimes also caused small changes of the lung blood volume but in most cases these were minimal (as e.g. in Fig 7). A measurable change was obtained in nine instances. Two showed a slight increase, seven a slight decrease. The mean change was −1 per cent, with a S.D. of 1.1.

Quantitative calculations. In Eq. II.3 $\Delta R/R$ was replaced by $\Delta|Z|/|Z_0|$ as the impedance was considered to be purely resistive. With the experimental set up used $\Delta|Z|$ $|Z_0|$ and V_A can be measured in absolute amounts, as can the ratio $\Delta V_E/V_E$. For each cat multiple regression calculations were made to find the coefficients of the equation

$$\Delta|Z|/|Z_0| = a_0 + a_1 \Delta V_A - a_2(\Delta V_E/V_E) \quad (II.4)$$

All procedures in which changes in lung blood volume and/or end-expiratory volume occurred were included in the calculations. These were carried out on a computer using a standard program for linear multiple regression equations. The results are shown in Table 1 where the separate set of coefficients is given for each cat. The values for V_A and $V_A/(V_A+V_E)$ were

Table I Regression coefficients f r three different cat and calcul ted V_A

$\Delta\|Z\|/\|Z_0\|$	$= -a_0$	$+ a\ \Delta V_A$	$- a_2\,(\Delta V_E/V_E)$	V_A
Cat III	0.18	0.19	0.26	137
Cat IV	0 09	0 00	0 13	14
Cat V	0 0	0 1	0.20	1 5

found by identification with Eq II.3 The volume V_A thus corresponds to a_2/a_1 and $V_A/(V_A+V_E)$ to a_2.

Discussion

The aim of the present study was twofold. The first was to evaluate whether the impedance measurements could detect the direction of changes in the ratio between the volume of air and the volume of blood in the lungs and the second aim was to test the validity of an equation used for the quantitative relationship between the impedance the volume of air and the volume of blood in the lungs

The experimental set up made it possible to follow changes of the transthoracic impedance as well as changes of the lung blood volume and the lung air volume simultaneously It must however be emphasized that the three variables were studied in three different parts of the lungs Changes of air volume in the lungs detected in this system emanated from the entire lungs while changes of the radioactivity (blood volume) were detected from a sharply limited cone of tissue in the sagittal plane over the base of the right lung The transthoracic impedance in turn, was monitored over a lung section essentially corresponding to a cylinder through both lungs in the frontal plane

Since the hydrostatic pressure differences are small in the parts studied, results obtained from the impedance and radioactivity measurements were assumed to be quantitatively representative of the whole lung

The detection of variations in the lung blood volume as measured by the radioactivity from one field over the thorax involves one possible fallacy This occurs if a major part of the activity detected is emitted from blood within the heart chambers and not in the lungs

This uncertainty was resolved in two differe ways After each experiment the thorax wa opened with the collimator in an unchange position and it was then directly seen that th heart chambers were not involved in the limite field of detection.

The experiments included periods of intra venous infusion of large doses of norepinephrine This agent produces both a very powerful con striction of the capacitance vessels of systemati vascular beds and reduces the end-diastolic an the end systolic heart volume (3) Under th influence of norepinephrine blood was the shifted from the systemic to the pulmonar circulation, while at the same time the volum of the blood in the heart decreased. Therefore when an increased radioactivity was recorded as in Fig 6 this implied that the activity wa emitted from lung tissue and not from the heart

The intention of the experiments was to var *the ratio air/blood within the lungs by a direct* change of only one of the components at a time In most instances this proved possible merely giving a minimal effect on the other Variations of the blood volume in some case produced too large effects on the tidal volume to be neglected On the other hand the end expiratory level remained remarkably constant in spite of large shifts of the lung blood volume (Fig 3) Therefore steady state levels of impedance and lung air volume were compared only at end-expiratory levels The time constant of the ratemeter did not permit an estimation of the variations in the radioactivity during one single breath

The results of varying the ratio air blood with different methods were consistent Regardless of whether the ratio was elevated by an increased amount of air or by a decreased amount of blood the TTI rose When the ratio fell because of a decreasing air volume or an increasing blood volume the impedance also fell. Thus, the impedance can be used to detect shifts in the ratio between the air and the blood volumes in the lungs

Since the basic impedance absolute change of impedance absolute change of air volume and relative change of blood volume were all directly recorded it was possible to solve the equation given in the introduction (Eq II:3)

The quantitative relationship between changes of impedance air volume and blood volume outlined in Eq. II 3 allows the calculation of values for the functional residual capacity (FRC) corresponding to V in the equation.

Table I shows similar values for FRC in the three cats. These values are somewhat higher than those arrived at by Crosfill and Widdicombe (1) However as pointed out by Radford (7) the method used by these authors is prone to underestimate the FRC The presented values agree closely with those calculated from Fig 2 and 3 in Radford's paper Thus the values for FRC that can be indirectly deduced from our series appear to agree reasonably well with previous scanty information on FRC in the cat

The data were also used for estimating the ratio $V_A/(V_A+V_B)$ in Eq II.3 This ratio allows an evaluation of the relative magnitude of the components in the impedance measured.

The change of the total impedance is related to a change of the blood volume with a reduction factor of $V_A/(V_A+V_B)$ The volume V_A is about 125 ml (Table 1) and V_B can be assumed to be about 50 ml. Thus the reduction factor should be expected to be around 0 8 However when measured it only amounted to 0 (a_2, Table 1). This implies then, that a major part of the impedance variable $|Z_0|$ measured transthoracically from side to side in the cat is derived from tissues with non-changing resistivity The lung tissue with a variable resistivity contributes with only one third of the total basic impedance $|Z_0|$ but with the total change of impedance in respiration.

The dat in Table I substantiate the view that measurements of transthoracic impedance gi quantitative information about the changes n the ratio air/blood in the lungs. However since the impedance measured from side to side in the cat also comprises a non negligible fraction of non changing impedance the calculations cannot be exact.

Summary

The assumption that measurement of the transthoracic impedance can be used to assess variations of the air/blood volumes in the lungs has been tested.

In cats transthoracic impedance lung blood volume and lung air volume were recorded separately and the blood and air volumes varied independently The results show that the transthoracic impedance sensitively detects changes in the ratio between lung air and lung blood volumes. It is further indicated that impedance measurements can be used for evaluation of the magnitude of changes in this ratio

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From the Department of Pediatrics, Children s Hospital, University of Göteborg, and the Research Laboratory of Medical Electronics Chalmers University of Technology Göteborg, Sweden.

Transthoracic Impedance
III Methodological Studies in Newborn Infants

by LARS VICTORIN WILLIAM DAILY and TORSTEN OLSSON

An increasing interest has arisen in the use of transthoracic impedance (TTI) techniques on newborn infants in monitoring for apnoea, a serious complication especially in the small prematures. The method has in this respect proved to be of clinical value (4 15 16 20) Particularly in adult medicine it has also been used to record the frequency of respiration and tidal volume (2, 6 7)

In the foregoing Parts I and II of this series it has been shown that with an apparatus fulfilling specific criteria, particularly with regard to insensitivity to variation in skin and contact impedance it is possible to record not only respiratory but also circulatory variables pertaining to the lungs, both statically and during respiration (11 14) In connection with the newborn this information is of great value. At no other time is the ratio air/fluid in the lungs, under physiologic conditions subjected to more dramatic changes than during the first day of life It is also well known that specific pathological conditions during the neonatal adaptation, e.g the hyaline-membrane-disease are characterized by considerable disturbances in both the respiratory and circulatory functions (1 3 9 18 10 1 23)

The present work deals with the results of the use of the TTI method on the newborn infant Practical and technical details of the application of the electrodes are presented concerning skin impedance baseline variation and choice of electrode position. On the basis of the hypothesis that this method gives information about the ratio air/fluid the effects of hydrostatic factors were studied by various electrode applications and varied positions of the infant. Furthermore, the relation between variations in air volume and impedance dynamically (i.e during respiration) is reported.

Methods

The instrument used to measure TTI was based on a four-electrode constant current half bridge having a 0.2 mA peak to-peak 50 kHz source (13) Measured values are the resistive part of the impedance. For conformity with our further studies measured values are presented as the magnitude of the impedance |Z| The error induced hereby is about two per cent of the absolut values (14)

For the recordings of simultaneous variations in the air volume during respiration a reverse plethysmograph according to Karlberg *et al* (10) was used.

Material

Studies were performed on clinically well infants from neonatal wards. The groups are specified more exactly in conjunction with the respective studies.

Skin impedance

An important factor in the design of the apparatus, and of the electrodes used, is to minimize the effect of contact and skin impedance The shape of the created electric field will change until a homogeneous current distribution

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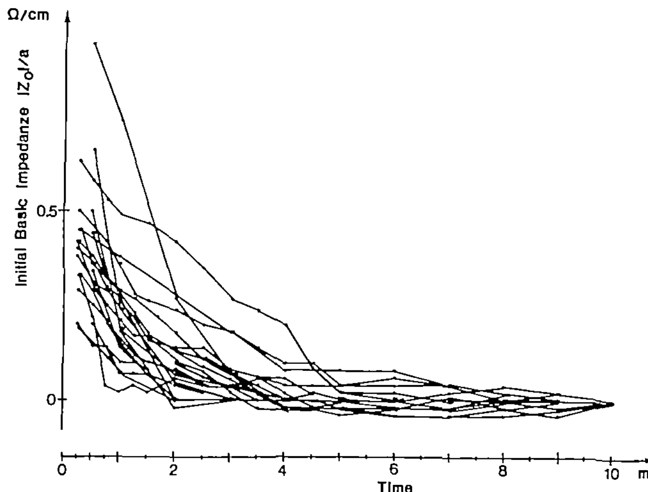


Fig 1 Initial change in the basic impedance $|Z_0|$ after electrode pplicat on to the skin xpressed in deviati from the value at 10 minutes after pplication. The mpedance values are corrected f interelectrode distance

has been established at the injection electrodes through the low conductive portions of the skin in contact with the electrode via the electrode paste This creation of a homogeneous electric field is thus dependent on the keratolytic, penetrating effect of the contact paste used in combination with the so-called floating electrodes (14)

In order to study the time-factor of this course a continuous monitoring of basic transthoracic impedance $|Z_0|$ was carried out on 20 infants aged between four hours and three days The recording was taken with the electrodes placed bilaterally in the mid axillary line of the mammillary plane The first reading was made as soon as possible which generally meant 10–15 seconds after the application of the first pair of electrodes Continued readings were then made during 10 minutes at short intervals accordi to Fig 1 In order to decrease possible effec of different inter-electrode distances, the resul are expressed in ohm/cm (cf below)

Results

The $|Z_0|$ level dropped during five minut following the application of the electrodes aft which no deviation from the 10-minute valu could be noted in the mean values The deviatio during the first few minutes was large bu gradually declined.

To judge from 95 per cent confidence interval the mean values at 4 5 minutes and later do not differ from the value at 10 minutes At 4 5 minutes the test is sufficiently reliable to reveal a deviation from zero of 0 02 ohm/cm with a probability of 80 per cent

No further significant change in impedance level occurs during the following two hours (22). An adult subject kept the electrodes in position for seven days without any change in $|Z_0|$ being noticed after the first few minutes.

Conclusion

For a detailed analysis of intrathoracic impedance variables in newborn infants the studies should not be commenced until five minutes after the electrodes are applied on the skin. On the other hand, if the purpose of the impedance recording is solely to obtain a serviceable signal for monitoring the frequency of respiration, immediate recording is possible.

Baseline variation

If the child moves violently with or without crying, the TTI will increase as shown in Fig. 2. Increased inspiratory volume with a temporary elevation of the end-expiratory level can be one explanation of this finding. However the same phenomenon is also noted without any change in the respiratory volumes, measured with the reverse plethysmograph. The reason for the increased impedance is then to be found i[n] vari[a]tions inside the lung, the subcutaneous tissue, the inter-electrode relation or the skin impedance, all of which can influence the shape of the electrical field. The relati[ve] importance of the various components, with respect t[o] these so-called movement artef[a]cts, has not been separately investigated.

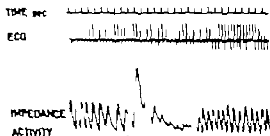


Fig. 2. Change in base impedance level [w]ith [a] moving infant. Durat[io]n of activity is marked at the bottom of the figure. It is noted [th]at [t]he initial impedance level is reached within [a] few seconds after ceasing of activity.

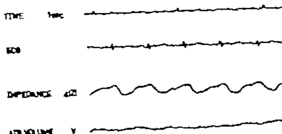


Fig. 3. Effect of cardiac activity on transthoracic impedance during an apnoea period.

Judging by the constant finding that the initial level is reached again within a few seconds, the electric field will regain its shape when the baby quiets down.

Conclusion

F[o]r quantitative analysis of the ratio air/fluid in the lungs by means of impedance recording, it is essential that the infants be relaxed and quiet at the examination.

Cardiac activity

The impedance curve in apnoea follows closely that of heart volume with a steep drop that agrees in time with rapid ventricular ejection, and slowly rising during diastole (Fig. 3). Redistribution of blood from the heart to the pulmonary vessels by the use of intravenous norepinephrine infusion causes a drop of the *TTI* (*11*). The heart proper becomes smaller during the systolic phase and increases its *resistivity*, indicating that the blood inside the heart has a smaller conductive value than th[e] same blood volume redistributed into the pulmonary circulation. This fact has been pointed out earlier by Nyboer (12).

Conclusion

Changes seen in TTI with heart beats are a function of a direct stroke volume effect with increase in blood in the pulmonary vessels.

Positioning of electrodes

The electrodes should be arranged *so that as* much as possible of the applied constant electric current will flow through *the tissue of* interest, in this case the lungs.

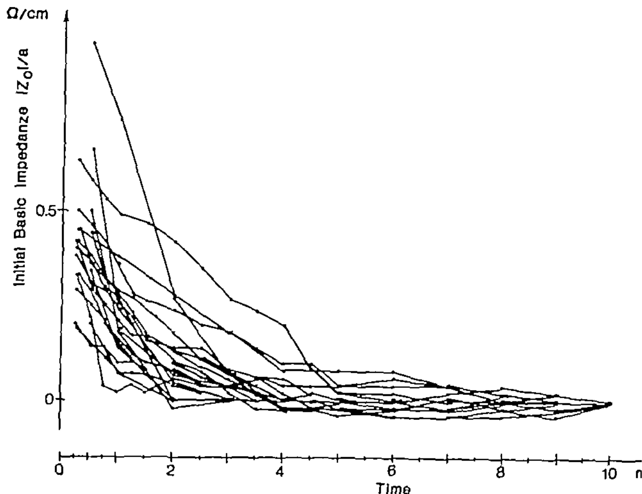


Fig 1 Initial change in the basic impedance $|Z_0|$ after electrode application to the skin expressed in deviat from the value at 10 minutes after application. The impedance values are corrected for interelectrode distance

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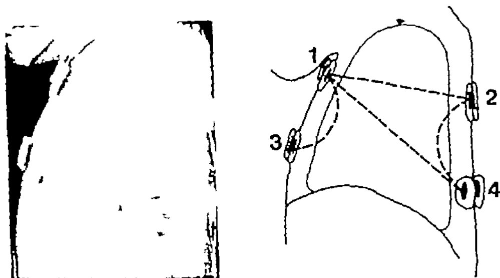


Fig. 5 Lateral view and schematic dra ing of an infant with electrodes applied to the front and back of the thorax (pairs 1 2, 3 and 4) Lead configurations used are marked by dashed lines between the respective electrode pairs.

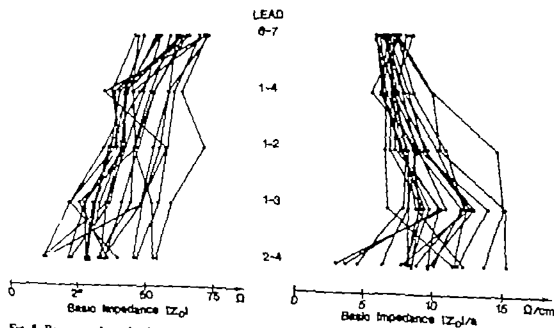


Fig. 6. Base impedance levels for all leads used, with and without correction for interelectrode distances. The values are connected to each other for each individual case



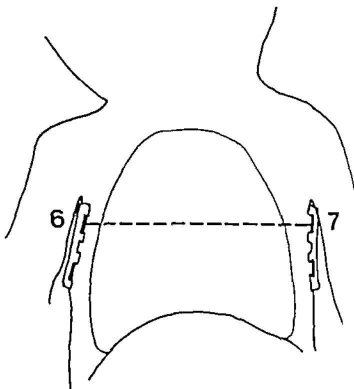


Fig 4 Frontal view and schematic drawing of an infant with bilateral application of electrodes (pairs 6 and 7).

Electric field measurements *in vitro* have shown that the intensity of electric current is most pronounced centrally along the connecting line between the injection electrodes progressively decreasing with the distance from this line (14) The electric field created is determined by the volume relations the position of the electrodes and the resistivity of the tissues involved. The epidermis and the fat layer of the skin serve to some extent as insulators due to their high resistivity similar to bone structures in the thorax (8 17) The lungs will strongly affect the TTI as their volume is large and resistivity comparatively low (8)

The effect of the size of the object on the impedance is very small, judging from calculations based on the electric field on the surface of spherical and cylindrical bodies and with symmetrically placed electrodes The impedance depends mainly of the distance between the injection electrode and the measuring electrode (14) For asymmetrical positioning of the electrodes or ellipsoid cross-section of the body to be studied, the influence of distance will increase In a practical examination of the importance of these factors with leads over the thorax a series of measurements was made with the electrodes placed in different positions.

Studies

Electrodes were applied on 20 babies as shown in Figs 4 and 5 The different pairs of electrodes were numbered and the recordings made according to the following arrangement

Straight sagittal over the upper portion of the right lung	(1–2)
Obliquely sagittal over the right lung	(1–4)
Transthoracic bilaterally in the mid-axillary line	(6–7)
Frontally over the right lung	(1–3)
Dorsally over the right lung	(2–4)

Results

A compilation of the individual results is given in Fig 6 showing the measurements of the basic impedance $|Z_0|$ using the various leads with and without correction for interelectrode



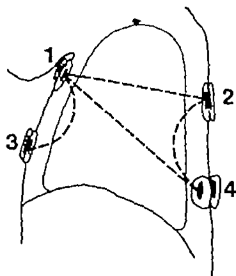


Fig. 5. Lateral view and schematic drawing of an infant with electrodes applied to the front and back of the thorax (pairs 1, 2, 3 and 4). Lead configurations used are marked by dashed lines between the respective electrode pairs.

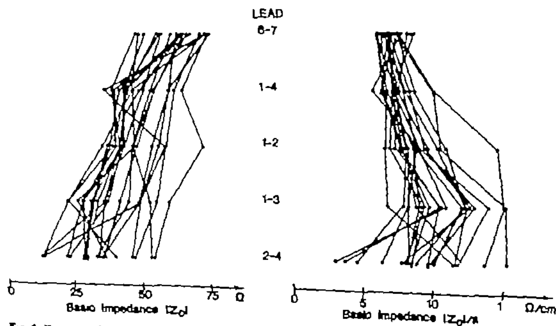


Fig. 6. Basic impedance levels for all leads used, with and without correction for interelectrode distances. The values are connected to each other for each individual case.

Table 1 Mean values and standard deviations (S.D.) of basic impedance $|Z_0|$ for the different leads given in absolute terms and after correction for interelectrode distances. Studies were performed in 20 infants with an age ranging from 1– 0 days.

Lead	Absolute		Corrected	
	Mean Ω	S D	Mean Ω/cm	S D
1–	47 0	0.0	8 0	1.8
1–3	39 1	10 5	11 0	3..
1–4	50 2	7.5	8 1	1 1
–4	3..4	9 1	11.8	3 1
6–	64 9	7	8 1	0 8

distance a Each point in the figures represents a mean value of three different measurements on each baby performed within a period of 30 minutes For the individual leads the mean values and the dispersions are given in Table 1

The mean of the maximal variation of the three measurements upon which each point has been based amounted to 1.0 ohm with an S D of 0 7

The minimal dispersion within the level of impedance among the various babies was obtained when measuring through the thorax (1–4 6–7) as compared to the situations when the electrodes were applied on the front or back of the thorax (1–3 2–4) The best agreement was found with the leads 1–4 and 6–7 after dividing with inter-electrode distance and between means of values from these *leads no significant* deviation was revealed

To judge from the figure some overcorrection does however arise for leads with longer inter electrode distances.

Conclusions

When specifying basic impedance correction for inter-electrode distance is valuable especially when different leads are compared

Effect of hydrostatic factors

As the blood is a main conductor in the lungs any existing hydrostatic dependent variations in the ratio *air/blood in various portions* of the lung have to be taken into account when selecting the positions of the electrodes For fast variations like those taking place on turning the infants change in interstitial fluid has been considered small and the change in the conductive compartment has been attribute to blood

Transthoracic leads

In 20 infants aged 1–20 days measurements were performed bilaterally along the mid axillary line (6–7) and with the electrodes placed along the anterior axillary line (8–9) The distance between the two pairs of electrodes on either *side of the thorax amounted to two cm.* The impedance was recorded with the baby in the supine position and after turning also in the prone position The lead 6–7 was situated at about the same level above the support in both positions while 8–9 in the supine position of the infant lay two cm above in the prone position two cm below lead 6–7

Results

There is a decrease in the impedance for lead 8–9 when turning the infant from the supine to the prone position (Table 2) This reduction is also significantly larger for 8–9 than for 6–7 and 8–9 is as compared to 6–7 displaced four cm further in a vertical direction

Conclusion

In the lungs of the newborn there is a hydrostatic influence on the ratio air blood which leads to a lower resistivity in a part of the lung closer to the ground.

Measurements dorsally and frontally over the thorax

Measurements were also performed using frontal (1–3) and *dorsal (2–4) leads* with the child in supine and prone positions respectively For anatomical reasons the distance between the pairs of electrodes in these positions became shorter than with transthoracic measurement In order to avoid artefacts due to the

Table 2. Mean change in basic impedance level, corrected for interelectrode distance on turning from supine to prone position and vice versa. Standard deviation (S.D.) and standard error of the mean (S.E.M.) are also presented. 20 infants are studied with three turns each. The table thus presents the results from altogether 60 instances for each lead.

Lead	Mean Ω/cm	S.D	S.E.M.
1–3	−0.75	0.73	0.16
2–4	−0.13	0.79	0.18
6–7	−0.09	0.22	0.05
5–8	−0.28	0.27	0.06
(5–8)–(6–7)	−0.20	0.28	0.06

the lower pair of electrodes is displaced together with the skin against the support thus altering the electric field, the babies were held up and turned. The series studied consists of the 20 children mentioned above.

Result

The results are given in Table 2. Lead 1 3 shows a significantly lower level of impedance in the prone as compared to the supine position. The dorsal lead –4 reveals no significant deviation on turning

Discussion

The bove-demonstrated gravity dependence of the ratio air/blood in the lungs is confirmed by lead 1–3 but not 2–4 One explanation is illustrated by Fig 5 which shows that for lead 1-3 the convexity of the thoracic wall allows the central flow of current to pass through the lung parenchyma while –4 mainly covers the soft and bony portions of the back. These portions lack non-conductiv space t be replaced by conductive material and thus react less t hydrost tic changes.

A similar situation i depicted in Fig where in one case recordings were taken with lead 1–4 nd also between electrode pair 4 and another pair applied t the epigastrium two cm caudal to position 3 The major portion of the electric field thus covered the liver instead of the

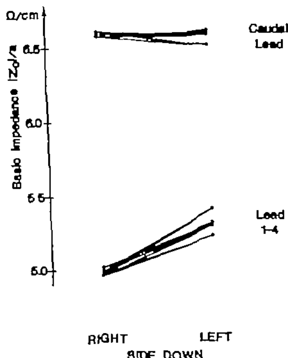


Fig. 7 Basic impedance values from turning of an infant with one lead corresponding t 1–4 (see text), the other composed of pair 4 and another pair placed two cm caudal to position 3 seen in Fig. 5. The infant was held with alternatingly the right and the left side upwards. The results are corrected for interelectrode distances.

lung The child was held above the support alternately with right and left side upwards. In accordance with the results mentioned the figure shows that a high position of the lung gives a high impedance, a low position a low impedance for lead 1–4 which again means that a lung situated in a low position contains comparatively more blood. In the caudal recording, no clear change of the impedance is noted on turning This is interpreted to mean that the liver structure is less gravity-dependent than the lung with its variable air compartment

Conclusion

The results confirm that the current applied passes through deep structures with transthoracic leads and that the observed hydrostatic variations are related to the the lung parenchyma.

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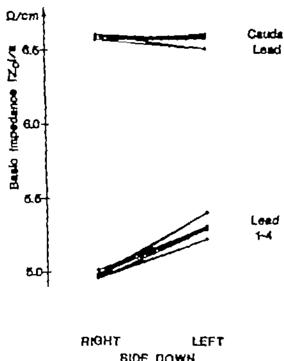


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Selection of electrode positioning for further studies

It is desirable that the impedance measured between the selected electrode pairs be representative of the lungs as a whole Transthoracic recordings are consequently preferable and among these leads 0–7 and 1–4 give the smallest dispersion, especially when corrected for inter electrode distance and for the following experiments these two were mainly used. With the baby in a supine position, lead 1–4 from the hydrostatic point of view represents a mean of the lung and the electric field of this lead chiefly covers the lung parenchyma Lead 1–4 was consequently considered to be best for the study of single breaths.

On turning the baby a comparatively small change of the impedance was found with lead 0–7 which suggested that this lead also seems to be favourable from the hydrostatic point of view An exact electrode positioning is of greater importance here however as compared with lead 1–4 The electric field in lead 0–7 runs through the mediastinum which does not vary in the same way with respiration as do the lungs This lead is therefore less suitable for studies on single breaths On the other hand when merely the changes in $|Z_0|$ are to be studied i e the level of end expiration this particular lead has several practical advantages especially for recordings of longer duration The electrodes are easy to apply bilaterally on the infant they can be observed during the entire recording and the risk of displacement of the skin with a change of the electric field is small

For the study of dynamic changes during respiration possible variation in the distance between the electrodes was investigated By means of cineradiograms it was found that when the infant breathed quietly the variation in distance from expiration to inspiration with lead 0–7 amounted to approximately three per cent while with lead 1–4 the figure was around one per cent A variation of this magnitude influences impedance less than one per cent (14 Eq I 10)

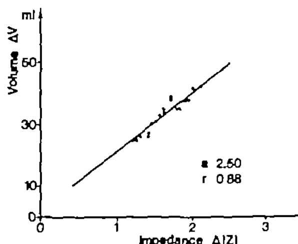


Fig 8 Correlation between air volume change ΔV and transthoracic impedance change Δ|Z| (lead 1–4) at different tidal volumes in one infant

Precision of the impedance determination

The above studies were furthermore used to evaluate the precision of the method In paired determinations of basic impedance from determinations in 60 newborns the mean difference was 0.53 ohm with a standard deviation of 0 44 No systematic difference was found. At the basic impedance of about 50 ohm the mean difference is thus about one per cent

Analysis of a breath

The relation between the change of impedance and of air volume was investigated at points of no flow at end-expiratory and end inspiratory level Fig 8 shows the lead 1–4 with a linear relation between impedance and air volume for tidal volumes from 20 to 40 ml Fig shows that the same relation exists for all leads examined (1–2 1–3 1–4 0–7 2–4) but with quantitative differences The least sensitive leads seem to be those from the front and the back of the thorax. If the impedance is corrected with respect to the distance between the electrodes it is found that the frontal lead 1–3 compares well in sensitivity with the transthoracic leads 1–2 1–4 and 0–7 while lead 2–4 still reveals a low sensitivity This finding conforms to our earlier interpretation that the

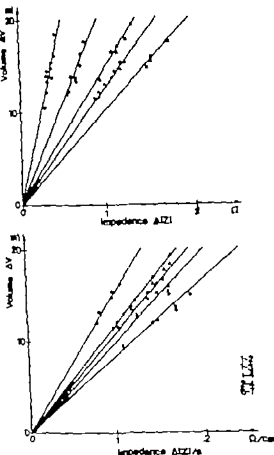


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electric field of lead 2–4 covers a smaller part of the lung parenchyma and therefore varies less with respiration.

The linear relationship demonstrated between the variation in impedance and air volume is pplicable to point of zero flow in maximal inspiration and expiration. If, instead, the entire breath is studied dynamically there is a relation existing between the two variables, as illustrated in Fig 10 A reasonable linearity exists between the variations of air and impedance during inspiration. In early expiration the pattern changes Despit a slowly decreasing volume of

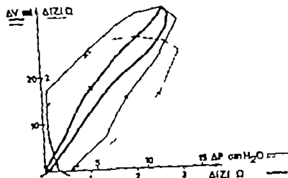


Fig. 10 An ordinary breath represented by the looped relationship between air volume change ΔV and oesophageal pressure change ΔP impedance change Δ|Z| and ΔP and finally the correlation between ΔV and Δ|Z|, marked by the heavy line in the figure

air in the lungs, the impedance rises which is interpreted as being due to a comparatively faster loss of conductive material (blood) from the lungs during this phase. In the rest of the expiration a linear relation between the variation in air and impedance re-commences. The above analysis will be the subject of further discussion in Part V of this series (5)

Summary

Studies have been performed on the use of the transthoracic impedance measuring technique on newborn infants The method permits the examination of the ratio air/blood in the lungs and the analysis of these changes by combination with measurements of variations in the air volume. To make this possible certain testing conditions must be fulfilled. With the technique used for this investigation, studies should not be started until the electrodes have been applied for fully five minutes and, further more the infant to be examined should be in a quiet state.

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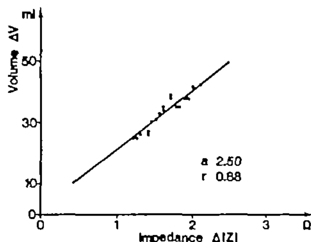


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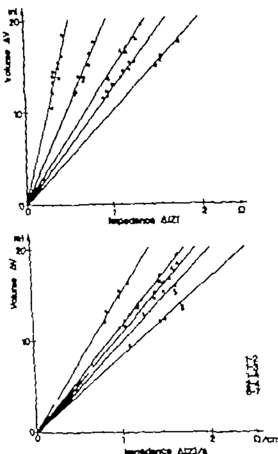


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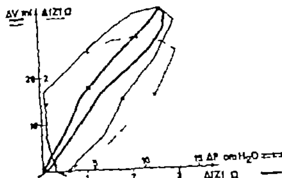


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The relation between differences in air volume *and the magnitude of impedance during respira*tion has been investigated Within wide ranges of the tidal volume there is a linear relation between these two variables when assessed at the moments of zero flow at end inspiration and end-expiration An analysis of the dynamic course during a breath however reveals a discrepancy between change in impedance and air volume interpreted as caused by simultaneous *variation in the blood volume* of the lungs

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Transthoracic Impedance
IV Studies of the Infant During the First Two Hours of Life

by LARS VICTORIN and TORSTEN OLSSON

The adaptation of the foetus to an independent life outside the uterus is a complex process involving dramatic and radical changes in the respiratory and circulatory systems. The first breath is initiated by an increased flow of sensory and biochemical impulses to the central nervous system. The airways and alveoli which were previously filled with fluid become expanded by the inspired gas, and the fluid is rapidly transported away through the upper airways, the blood vessels and as lymph via the interstitial space (2, 13 27). After the commencement of air breathing the blood circulation through the pulmonary vessels increases as the pulmonary vascular resistance declines and the right-left shunts through the foramen ovale and the ductus arteriosus gradually decrease (1 4 6 7 10 20 21 24 30).

There are many conditions which can cause disturbances in the initial adaptation. Examples are central depression caused by anaesthetic agents, malformations in the respiratory or circulatory syst ms, and factors promoting the development of the hyaline-membrane-disease in which both respiratory and circulatory components are involved (5, 1., 22 23 25). A further factor affecting the post natal adaptation is the magnitude of the placental transfusion, which has an influence, inter alia, on the total blood volume the haematocrit and the mechanics of respiration (16 18, 28).

Hitherto knowledge of immediate post-natal changes in pulmonary fluid volume in man is limited (3).

Our earlier investigations have proved that transthoracic impedance (TTI) is a function of the amount of conductive fluid in deep structures between the electrodes (14 70). The method is clinically simple and allows the ratio air/fluid to be studied in the initial adaptation period of the infant in an atraumatic way. This contribution presents the TTI measurements made on infants during their first two hours of life and after early or late clamping of the umbilical cord. When the studies begin, the infant is 15 minutes of age. At this time the total blood volume in the late-clamped infants (LCI) is about 30 per cent higher than in the early-clamped infants (ECI) (28).

Material

The series included 20 newborn infants with early clamping and 20 with late clamping of the umbilical cord. For infants in the first group, the umbilical cord was clamped before the first breath and within 10 seconds after birth. As LCI were considered those where the placenta and the child had not been separated until five minutes after birth and, furthermore where the placenta had been kept on the same or slightly higher level than that of the infant. In no case was the early clamping induced primarily for obstetrical reasons. All babies were born after uneventful term pregnancies and vaginal deliveries, the mothers receiving only intermittent N_2O analgesia (25% O and 75% N_2O) for pain relief. The newborn infants were in good condition, not requiring resuscitation or extra oxygen after delivery and

Table 1 Means and ranges for birth weight and gestational age for the three groups of infants studied ECI = early-clamped infants, LCI = late-clamped infants, CG = control group.

Group	Birth weight Mean grams	Range	Gest age Mean week	Range
ECI	3560	3000–4670	40	39–43
LCI	34*0	*860–4*00	40	30–43
CG	100	1000– 550	36	31–40 5

the further post natal courses were uncomplicated

Twenty clinically healthy infants treated at the neo-natal nursery due to low birth weight were used as a control group Their mean age was 15 days ranging from 4–32 days These infants were considered to have passed the period of rapid postnatal adaptive changes in pulmonary and circulatory function The group was otherwise heterogeneous consisting of both *appropriate for-date and small for-date babies* Means and ranges for birth weight and gestational age in the babies of the three groups are found in Table 1

Methods and procedures

Immediately after birth the newborn infants were placed in a drainage position with the head lower than the rest of the body and the mouth and hypopharynx were gently suctioned free of fluid After clamping of the cord, according to the principles described the babies were placed horizontally in a supine position.

The impedance apparatus used is based on a four electrode constant current half bridge with a 0.2 mA peak to-peak 50 kHz source (19). TTI *recordings were made with the electrodes* applied bilaterally in the mid-axillary line when the infant was 10 minutes old After allowing the electric field to become stabilized for five minutes (20) the first recording was taken at 15 minutes and thereafter at set intervals up to 120 minutes It was possible to make the reading within 30 seconds from the time set except in two instances when a stable value could not be *arrived at due to extreme movements on the* part of the subject The results of the determinations and inter-electrode distances are presented in Tables 2 and 3

T ble Ba o mpedance $|Z_0|$ (ohm) and inter-electrode distance Late-clamped infant (LCI).

C se no	Minutes 15	*0	_5	30	45	60	73	90	103	1*0	cm
1	53 4	53 0	5	51 0	50 4	49 6	49 0	49 4	50.0	50 8	10.5
	40	39 9	38 0	38 4	38.0	3 6	38.0	38 4	38.8	39 0	9 5
3	00 4	59 8	59 4	59 0	58.4	5 6	57 0	57 4	5 8	58 4	9.5
4	5 0	5	51 4	50 0	50 6	51 0	51 0	51.2	50 8	50 4	9.0
5	47 4	40.4	45.	—	45 6	46 0	46 4	40 8	47 0	47 0	10 0
6	48 4	47 6	46 8	46.6	47 4	47 8	48	48 8	40 0	49 0	9.5
7	50 0	49 2	48 6	47 8	47	47 0	4 6	48	48 8	49 2	9.5
8	60 8	50 6	58 8	59 0	58.8	59 0	59 8	59.2	59 0	59 4	12 0
9	61 6	61 0	61 6	61.2	60 4	59 6	50 4	60 0	60.2	60 0	11 0
10	47 0	40.4	46.0	45 8	46 0	46 2	46._	46 6	47 0	4 0	12 0
11	03 8	03 0	62 0	62 8	63.0	62.8	62 8	63 0	03 0	63.2	10 5
1	56 2	55 0	54 8	54 4	54 0	54 2	54 0	53.8	53 6	53 8	10 0
13	58 0	57.2	57 0	56 8	56.2	56.0	56.4	56.8	57._	57 6	10 0
14	5 .2	51 0	50 6	50 0	49 8	49 8	50 0	49 8	50 2	50 8	10 5
15	46.2	45 6	44.8	44 0	43 3	4 .2	4_0	41 6	41 4	41 6	9 0
16	53.2	5 4	52.2	51 8	5_0	5 4	53.0	53 0	53.4	53 0	10 0
17	52._	51 6	51 0	50._	40 6	50 0	50.8	51 0	50.6	51 0	10 0
18	6_0	61 6	61 6	61 0	60.	60 0	50 6	59 0	59 8	60 4	10.0
19	63.8	63.0	6_6	61 8	61 6	61 0	61 4	61 6	62.0	61 6	9 0
0.	54 0	53.4	53 0	52.2	52.0	51 6	51._	51 8	5_4	53 0	10 0

Table 3. Basic impedance $|Z_0|$ (ohm) and inter-electrode distance. Early-clamped infants (ECI).

Case no.	Minutes 15	20	25	30	45	60	75	90	105	120	cm
1	73.1	72.5	71.3	70.2	69.6	69.0	69.7	69.9	70.0	70.5	11.0
2.	59.8	59.8	—	57.8	57.2	55.8	55.8	56.0	54.2	54.0	11.0
3	58.2	57.0	56.2	55.6	55.3	54.0	54.3	54.5	54.4	54.6	11.0
4.	66.0	65.2	64.3	64.7	63.8	64.0	64.2	63.6	64.0	64.8	11.0
5.	53.8	52.8	52.0	51.8	51.3	51.4	51.2	51.0	50.8	50.6	11.0
6.	66.4	65.0	64.5	64.4	64.6	64.4	64.0	64.3	64.8	64.8	11.0
7	64.0	63.2	62.8	62.0	61.2	60.6	61.0	60.8	60.0	61.3	11.0
8	54.5	53.4	53.0	53.3	52.8	53.0	53.3	53.4	53.8	54.4	11.0
9.	64.8	64.0	63.6	63.4	63.2	63.4	63.6	63.8	64.4	63.8	11.0
10	56.4	55.8	55.2	54.8	55.0	54.6	54.8	55.2	55.0	55.4	12.0
11.	63.8	64.0	63.6	63.4	64.0	64.2	64.6	65.0	64.8	65.0	11.8
12	53.8	53.6	53.2	53.0	53.6	53.8	54.0	53.8	54.2	54.0	11.0
13.	57.8	57.4	57.0	57.2	57.4	57.3	57.4	57.6	57.4	57.4	10.0
14	59.4	58.5	58.4	58.2	58.4	59.0	59.2	59.4	58.6	59.8	10.0
15.	67.2	66.4	66.0	65.2	64.8	64.2	64.4	64.6	64.6	64.8	11.0
16.	67.6	62.2	62.0	61.8	61.4	61.6	61.4	61.2	61.4	61.6	10.5
17	50.8	50.0	49.8	50.0	50.4	50.8	50.4	51.0	50.8	50.6	10.0
18.	48.0	48.6	48.6	46.0	44.4	48.3	48.8	48.8	49.0	49.2	12.0
19	59.8	59.2	58.8	58.4	58.0	57.8	57.8	56.2	56.2	56.4	11.8
20	54.8	54.0	53.4	53.0	52.8	52.8	53.3	53.8	53.8	54.3	10.0

Table 4. Basic impedance $|Z_0|$ (ohm) and inter-electrode distance. Control group (CG).

Case no.	Minutes 15	20	25	30	45	60	75	90	105	120	cm
1	50.4	50.0	50.7	51.2	51.0	51.2	50.8	50.6	50.4	50.8	12.0
2.	48.8	47.0	47.2	47.3	47.6	47.2	47.8	47.7	47.8	48.0	11.0
3	54.6	53.6	54.2	54.6	54.2	54.4	54.8	54.8	54.8	54.2	10.0
4	64.2	64.4	64.6	64.4	64.0	64.6	65.0	64.8	65.0	64.8	9.0
5	64.2	64.4	64.2	64.6	64.6	64.4	64.0	64.6	64.0	63.8	10.5
6	44.0	43.8	43.4	43.6	44.0	44.2	44.0	43.6	44.0	43.8	10.0
7	63.2	63.6	63.4	63.6	63.8	67.6	—	—	—	—	10.0
8	69.4	65.2	66.0	68.3	69.4	69.0	68.2	69.0	67.8	66.0	9.5
9.	50.6	50.8	50.4	50.6	50.8	50.8	50.4	50.6	50.6	50.4	9.6
10	37.0	37.1	—	37.4	—	36.8		37.7	—	36.0	10.0
11	65.8	55.9	58.8	50.3	—	57.8	—	57.9	—	—	10.0
12	46.8	47.0	46.8	46.5	47.0	48.8	—	—	—	—	9.0
13	42.3	43.2	42.8	42.8	42.2	42.8	—	—	—	—	9.0
14	67.8	55.0	56.2	59.0	48.2	56.2	58.0	37.8	58.0	58.0	10.0
15	54.2	53.6	53.0	53.6	53.8	53.4	53.6	53.6	53.4	53.2	9.0
16.	43.0	42.3	42.4	43.4	42.2	43.0	43.2	—	—		9.5
17	51.2	51.2	51.4	51.2	51.4	51.2	51.0	50.8	50.6	51.0	9.0
18	49.2	51.6	51.6	51.8	51.8	51.8	52.0	51.6	51.8	49.2	9.0
19	51.6	49.0	49.0	49.2	49.0	49.0	49.8	—	—	—	9.4
20.	50.6	49.3	49.5	49.6	49.8	50.0	49.8	49.6	49.6	51.2	9.0

Table 5 Statistically estimated values of μ and α in Eq IV... for LCI and ECI confidence intervals at th 95 per cent level.

	μ	α
ECI	0 16 ±0 03	0.57±0 10
LCI	0..1 ±0 01	0 03±0 06
LCI ECI	0 033±0 051	0 06±0 13

In the control group the first recording was made five minutes after the application of the electrodes on the infants and then at the same intervals as in the other groups Due to factors not connected with the baby the studies in six cases were ended before two hours had elapsed (Table 4)

The magnitude of impedance obtained in the quiet infant at end-expiratory level i e corresponding to the functional residual capacity FRC was determined and called basic impedance $|Z_0|$

Analysis of results

The impedance values measured are for the calculations and in Fig 1 divided by inter electrode distance a to decrease possible effects that the distance may have on the results (20)

The measurement results for LCI and ECI from 15–60 minutes have been tested against a mathematical relationship with t in minutes after birth

$$|Z_0|/a(t) = |Z_0|/a(15) + \mu(e^{\beta(0.2t-3)} - 1) \qquad (IV.1)$$

If this formula is valid the deviation from the initial figure for the infants will follow the equation

$$|Z_0|/a(t) = \mu(e^{\beta(0.2t-3)} - 1) \qquad (IV.2)$$

The statistical assessments of μ and $\alpha = e^{\beta}$ are given in Table 5 together with confidence intervals for the two parameters. All significances and confidence intervals given in this work refer to the 95 per cent level.

Results

The change in the impedance level is depicted in Fig 1 In all the cases studied immediately after birth both ECI and LCI a significant reduction of $|Z_0|$ was noted from 15 to 30 minutes. The LCI group declined further and remained at a lower level than the ECI group during the period 45–75 minutes post partum, as apparent from the graph During the second hour of life the $|Z_0|$ augmented in the LCI while the ECI did not show any significant change

The parameter μ in the mathematical formula, approximately corresponding to the level at 60

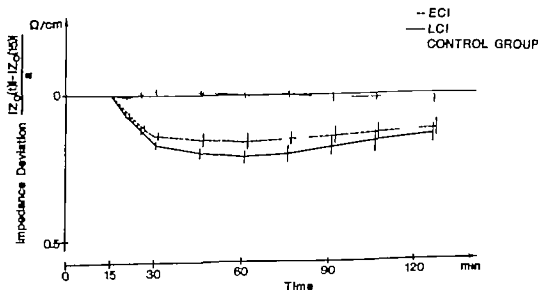


Fig 1 Change in basic impedance (Means ± S.E.M.) corrected for interelectrode distances. Starting point f the recordings, 15 minutes, corresponds for the control group to f ve minutes after the pplication of the electrodes.

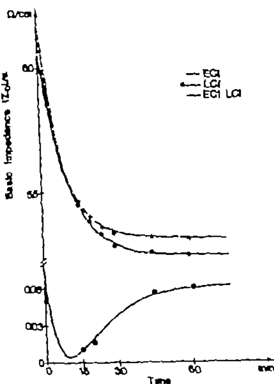


Fig. 2. Basic impedance (Z_0) corrected for interelectrode distance (a) as calculated from Eq. IV 1 for the different groups and the differences between the groups. Means of the measured values are plotted.

minutes shows a significant difference for both groups while the parameter α does not differ significantly. Theoretical values obtained from the mathematical formula IV 1 with assessed μ and α values are inserted in Fig. 2 together with the differences between the groups. The values have furthermore been extrapolated backwards to the time of birth.

In the infants belonging to the control group, there is no significant deviation from zero during the two hours of study.

Discussion

The transthoracic impedance allows an estimation of the conductive material in the lung parenchyma. The recording is however the net result from compartments in the lung with different electric characteristics and no direct separation between them can be made (19, 20).

All newborn infants both LCI and ECI showed an initial drop in impedance after the start of the recording 15 minutes after birth levelling off after the first half hour to increase, at least in LCI, during the second hour.

Interpretation of these findings requires that consideration be given the changes in volume factors involved in the creation of the impedance signal.

The initial stage of air filling of the lungs is extremely fast. Already with the first few breaths there is created a functional residual volume (FRC) which according to Klaus (16) increases to stabilize at a level of around 30 ml per kg body weight at 30 minutes of age. Other authors have found a somewhat longer time of increase between one and three hours (11, 26). Oh *et al.* (18) examining ECI and LCI separately noticed a lower FRC for LCI during the first six hours of life. No information appears to be available concerning the longitudinal change in FRC for LCI and ECI separately.

Gas exchange over the alveolar membranes requires elimination of the bronchial fluid produced pre-natally and filling the alveoli. When the thorax is compressed during the act of delivery (13) and also when adequate drainage and suction are performed post partum, some of this fluid disappears via the airways.

Animal experiments have proved that an essential part of the bronchial fluid is transferred into the pulmonary interstitial space and from there drained through the lymphatics. As studied in the newborn rabbit ( ) periarterial lung tissue rapidly becomes distended with fluid after the start of breathing, to reach a maximum at 30 minutes of age after which time a gradual decline of the distension is noted during the ensuing four hours. The lung lymph drainage in the lamb increases markedly already in the first few minutes after birth. An amount of lymph corresponding to one third of the volume of fluid and the entire amount of protein lost from the lungs was collected from the thoracic duct during the two first post natal hours (27). Corresponding to

Table 5 Statistically estimated values of μ and α in Eq IV:2 for LCI and ECI confidence intervals at the 95 per cent level.

	μ	α
ECI	0.16 ± 0.03	0.57 ± 0.10
LCI	0..1 ± 0.04	0.63 ± 0.06
LCI-ECI	0.053 ± 0.051	0.06 ± 0.13

In the control group the first recording was made five minutes after the application of the electrodes on the infants and then at the same intervals as in the other groups. Due to factors not connected with the baby the studies in six cases were ended before two hours had elapsed (Table 4).

The magnitude of impedance obtained in the quiet infant at end-expiratory level i.e. corresponding to the functional residual capacity FRC was determined and called basic impedance $|Z_0|$.

Analysis of results

The impedance values measured are for the calculations and in Fig. 1 divided by interelectrode distance a to decrease possible effects *that the distance may have on the results (29).*

The measurement results for LCI and ECI from 15–60 minutes have been tested against a mathematical relationship with t in minutes after birth

$$|Z_0|/a(t) = |Z_0|/a(15) + \mu(e^{\beta(0.2t-3)} - 1) \qquad \text{(IV 1)}$$

If this formula is valid the deviation from the initial figure for the infants will follow the equation

$$|Z_0|/a(t) = \mu(e^{\beta(0.2t-3)} - 1) \qquad \text{(IV 2)}$$

The statistical assessments of μ and $\alpha = e^{\beta}$ are given in Table 5 together with confidence intervals for the two parameters. All significances and confidence intervals given in this work refer to the 95 per cent level.

Results

The change in the impedance level is depicted in Fig. 1. In all the cases studied immediately after birth both ECI and LCI, a significant reduction of $|Z_0|$ was noted from 15 to 30 minutes. The LCI group declined further and remained at a lower level than the ECI group during the period 45–75 minutes post partum, as apparent from the graph. During the second hour of life the $|Z_0|$ augmented in the LCI while the ECI did not show any significant change.

The parameter μ in the mathematical formula, approximately corresponding to the level at 60

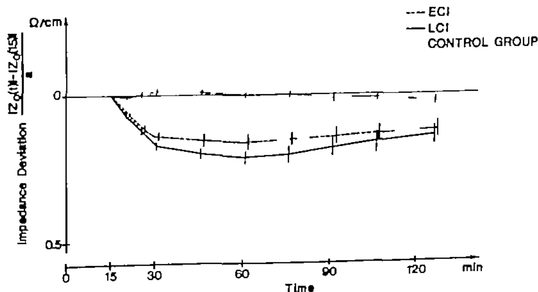


Fig. 1 Change in basic impedance (Means ± S.E.M.), corrected for interelectrode distances. Starting point for the recordings, 15 minutes, corresponds for the control group to five minutes after the application of the electrodes.

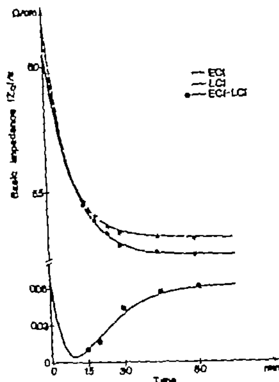


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minutes, shows a significant difference for both groups while the parameter α does not differ significantly. Theoretical values obtained from the mathematical formula IV 1 with assessed μ and α values are inserted in Fig 2 together with the differences between the groups. The values have furthermore been extrapolated backwards to the time of birth.

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The statistical assessments of μ and $\alpha=e^{\beta}$ are given in Table 5 together with confidence intervals for the two parameters All significances and confidence intervals given in this work refer to the 05 per cent level

Results

The change in the impedance level is depicted in Fig 1 In all the cases studied immediately after birth both ECI and LCI a significant reduction of $|Z_0|$ was noted from 15 to 30 minutes. The LCI group declined further and remained at a lower level than the ECI group during the period 45–75 minutes post partum as apparent from the graph During the second hour of life the $|Z_0|$ augmented in the LCI while the ECI did not show any significant change

The parameter μ in the mathematical formula approximately corresponding to the level at 60

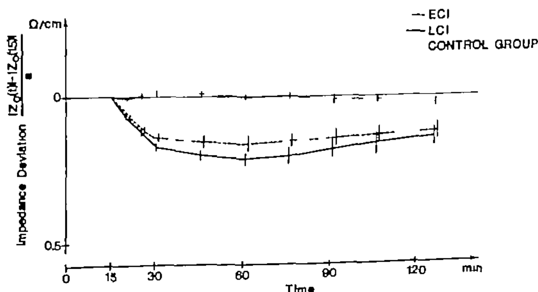


Fig 1 Change in basic impedance (Means ± S.E.M.), corrected for interelectrode distances. Starting point for the recordings, 15 minutes, corresponds for the control group to five minutes after the application of the electrodes.

the foetal shunts. A contributing effect from increasing interstitial fluid is also suggested.

After the first half hour of life a stabilization of $|Z_0|$ is noted. The FRC is possibly still increasing but at a relatively slow rate. A net drainage of interstitial fluid tends to diminish the interstitial space working to increase $|Z_0|$. With the virtually unchanged $|Z_0|$ found, progressive increase of pulmonary blood volume obviously counteracts the effects of possible rise in FRC and shrinkage of the interstitial space during the time between 45 and 75 minutes after birth.

The increasing $|Z_0|$ noticed in LCI during the second hour of life can be regarded as the net result of several parallel phenomena. The FRC is lower after late clamping of the umbilical cord and may be increasing in LCI. These infants also have a relative intravasal load which, especially during the first few hours, is counteracted by loss of plasma into the extra-vascular space, with a reduction of total blood volume (9, 17, 28). Left atrial pressure falls in LCI during the same time which, in accordance with the rise in $|Z_0|$, may indicate also a falling pulmonary blood volume. Finally as judged from the findings in newborn rabbits (2), the distension of the interstitial space declines. Despite the fact that the possible change in these three factors, namely increasing FRC, decreasing pulmonary blood volume and decreasing interstitial space, all qualitatively affect the $|Z_0|$ towards an increase, the initial level at 15 minutes of age is not reached during the time of the study.

The condition is more stable for ECI and the impedance does not change significantly during the second hour.

Summary

The initial functional adaptation has been studied with the transthoracic impedance measuring technique in infants from 15 minutes to two hours of life. The series consists of 20 newborns with early and 20 with late clamping of the umbilical cord.

All infants showed a marked fall in basic impedance $|Z_0|$ between 15 and 30 minutes of age. From 45 to 75 minutes $|Z_0|$ was virtually unchanged, at a level somewhat lower for the late-clamped group. During the second hour a rising $|Z_0|$ was noted in the same group.

With the aid of a mathematical formula an extrapolation backwards from 15 minutes to the time of birth was made for $|Z_0|$. The results obtained directly and after the extrapolation are discussed together with previous known facts about the adaptation process in animals and infants.

Main factors influencing $|Z_0|$ are air filling of the lungs, pulmonary blood volume and pulmonary interstitial fluid volume. The dynamic interplay between these variables during the first hours is discussed.

The results suggest a pronounced increase of pulmonary blood volume and pulmonary interstitial fluid volume during the first half hour of life, simultaneously with the establishment of a functional residual capacity of air in the lungs.

That infants with late clamping of the umbilical cord fall to a lower level of $|Z_0|$ for the time period from 45 to 75 minutes is interpreted as reflecting a larger pulmonary blood volume in combination with a smaller functional residual capacity as compared with the early-clamped group. A rise in $|Z_0|$ for late-clamped infants during the second hour of life points in the direction of an approximation between the two groups as pulmonary fluid and blood decreases and functional residual capacity increases in the late-clamped group.

No significant changes in transthoracic impedance were found in a control group of newborns past the post-natal period of early adaptation to extra-uterine life.

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the start of shrinkage of the interstitial space after the first half hour a slight fall in the lymph flow out of the lungs was noted but it was still high at two hours when the interstitial shrinkage was marked *Analysis of inter alia* the protein content of the lymph makes it reasonable to judge the lymph as consisting mainly of bronchial fluid (27) It is furthermore probable that part of the bronchial fluid is drained directly to the capillaries lining the alveoli this factor has however not been possible to quantify

With air filling of the lungs the pulmonary *vascular resistance decreases pulmonary blood* flow increases and the pressure in the pulmonary artery falls successively (4 6 7 8 22 23) Consequently the blood will be progressively directed to the lungs with a diminishing right to-left shunt through the foramen ovale and ductus arteriosus and for a period shifting over to mainly left to-right shunting The time factor in this sequence of events is by no means *the same for different infants*

In the individual case the direction and size of the shunts may vary with the oxygen tension in the blood with respiration and with cardiac cycle (1 6 7) In general a right to-left shunt of functional importance is noted only in the immediate postnatal period progressively decreasing during the first hour (10 23 30) The left to-right shunt is comparatively constant during the *first few hours to disappear some* time during the latter part of the first day of life

The important factor concerning TTI is volume and not shunt or flow directly An increase of flow in combination with the decrease in pulmonary vascular resistance causes with all probability an *increment* of pulmonary blood volume.

Obviously $|Z_0|$ is a function of the three variables air volume interstitial fluid volume and blood volume in the lungs The first characteristic change in $|Z_0|$ is the fall from 15 to 30 minutes of age An increase of FRC takes place during this period *tending to increase* impedance The actual change is a decrease which shows that the fluid factors have to more than compensate the effect of growing FRC

As judged from the animal studies (* *) *expansion of the interstitium* continues during the first half hour and the fluid is considered to originate mainly from inside the alveoli. It is important to stress that fluid inside the alveoli is less conductive as compared with the same amount of fluid situated in the interstitial space which means that a transfer of fluid from alveolus to interstitium will per se lower $|Z_0|$ (10)

An increase of pulmonary blood volume occuring as the right left shunt decreases, works in the same direction and we thus have two possible means of explaining the impedance drop as an increment of total pulmonary extra alveolar fluid.

For further analysis in order to differentiate between these two variables Eq IV 1 has been used (Fig 2) No significant difference between $|Z_0|$ in LCI and ECI was *found* at 15 minutes of age When the impedance course is extrapolated backwards to the time of birth, in accordance with the proposed equation the ECI will initially have a higher $|Z_0|$ which falls faster during the first 15 minutes, but stops at a higher level than the LCI

A haemodynamic explanation of this difference in behaviour between LCI and ECI *is possible* The well known fact of a smaller total blood volume in ECI (0 17 28) implies a higher initial impedance level due to a smaller pulmonary blood volume as well During the first half hour of life a constriction of the peripheral vascular bed in ECI distributes blood to the central circulation with a com*paratively faster increase in pulmonary* blood volume The fall in $|Z_0|$ ceases at a higher level as compared to LCI being limited by the smaller total blood volume

On the basis of our findings it is plausible that the change of *impedance found* during the first half hour of life reflects a gradual increase in the pulmonary blood volume due to decreasing right left shunting through

the foetal shunts. A contributing effect from increasing interstitial fluid is also suggested

After the first half hour of life a stabilisation of $|Z_0|$ is noted. The FRC is possibly still increasing but at a relatively slow rate. A net drainage of interstitial fluid tends to diminish the interstitial space working to increase $|Z_0|$. With the virtually unchanged $|Z_0|$ found, progressive increase of pulmonary blood volume obviously counteracts the effects of possible rise in FRC and shrinkage of the interstitial space during the time between 45 and 75 minutes after birth.

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Transthoracic Impedance.

V Effects of Early and Late Clamping of the Umbilical Cord with Special Reference to the Ratio Air to-Blood during Respiration

by WILLIAM DAILY[1] TORSTEN OLSSON and LARS VICTORIN

Studies on normal or pathological functional respiratory-circulatory adaptation in the immediate neonatal period are comparatively easy to conduct in so far as respiration is concerned. It is more difficult to obtain information about the circulatory variables such as pulmonary blood volume and flow with methods currently used in adult medicine. One main error is created by persistence of foetal shunts especially during the first day of life (6 7 11 15 26 27 29 37 38 45) The possible difficulties could be overcome by complex techniques in special laboratories (15 45) but an easily applicable method for the study of neonatal circulation fills an obvious need in research and clinical practice

From our previous theoretical discussions and animal experiments (21 34) it is concluded that transthoracic impedance (TTI) is a function of the ratio air/fluid in the part of the lungs situated between the measuring electrodes. Any electrical current applied will tend to traverse the thoracic cage mainly through fluids that do not involve hindering biological membranes (34). This implies blood lymph and interstitial fluid to be the main conducting media while air or any other gas inside the alveoli and bronchi is non-conductive. Intra-alveolar fluid, lung parenchyma cells, skin and other tissue conduct a minor part of the current (4 14 34 38). However skin and other tissue represent a relatively constant part of TTI as long as the electrodes are kept in the same position. Intra pulmonary gas and intravasal pulmonary fluid on the other hand are factors that may vary together or independent of each other and thus influence TTI (21)

The aim of the present study is to investigate by means of the TTI technique differences in the pulmonary fluid volume and the blood kinetics during breathing between groups of newborn infants who are in the process of functional physiological adaptation. Groups of infants with early and late clamping of the umbilical cord were selected since early clamping according to the principles described below is known to lead to a significantly lower total blood volume as compared with late clamping (30 43)

By comparing TTI with simultaneous recordings of air volume and oesophageal pressure change, correlations between variations in pulmonary gas and fluid compartments and lung mechanics were investigated.

Material

Studies were performed on seven newborn infants with early clamping of the umbilical cord (ECI) and on seven late-clamped infants (LCI) They were all full term vaginal spontaneously delivered babies with an uneventful perinatal course. The mothers were given intermittent N_2O analgesia (25% O_2, 75 N_2O) for pain relief No baby required resuscitation or

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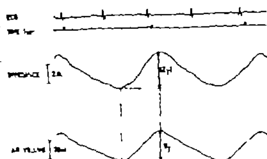


Fig 1. Change in air volume and impedance during respiration. Points of zero flow in end-expiration and end inspiration on the volume curve are marked on the impedance curve.

V_T = tidal air volume.
$|Z_T|$ = tidal impedance

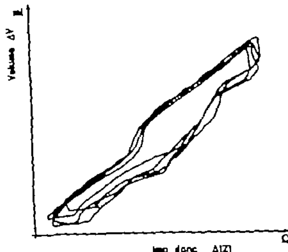


Fig. 2 Four consecutive breaths graphically represented in the form of respiratory loops from change in air volume and impedance.

Blood for haemoglobin and haematocrit deter minations was obtained from temporal artery puncture as described by Thomsen (41) the reason for choosing this site being that blood gas studies were made on the same samples.

As reference level for TTI was chosen the impedance at end-expiration and this variable was called basic impedance $|Z_0|$. A correction for interelectrode distance a was made in accordance with earlier considerations (44).

The records were analyzed as follows. The relation between the impedance deflection for a breath, tidal impedance $|Z_T|$ and tidal volume V_T was determined for inspiration by marking off the zero flow points on the respiratory curve on to the impedance curve and measuring the magnitude of the two (Fig. 1). Hence $|Z_T|/V_T$ represents the impedance change per unit air volume in inspiration. As shown previously in Part III of this series this is essentially linear change in the range of V_T used by the new born during quiet breathing (44).

For the relative impedance variation $|Z_T|/(V_T \cdot |Z_0|)$ the effect of variations among the individual cases on the shape of the electric field is reduced. This ratio, $|Z_T|/(V_T \cdot |Z_0|)$ is furthermore directly applicable in the theoretical equation concerning impedance change with a varying ratio air/fluid in the lungs as presented earlier (1 34).

During the breath the relationship $\Delta|Z|$ to ΔV describes a loop rather than a straight line mainly due to a delay in the fall of impedance at commencement of expiration.

A series of consecutive typical breaths is shown in Fig 2. This phenomenon is also illustrated in Fig 3: a proper amount of the impedance signal is subtracted from the air volume signal so that end-expiratory and end-inspiratory levels will approximate the same baseline. To obtain a representation of this loop configuration we selected the point of half inspiration on the

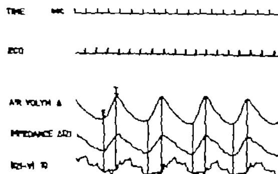


Fig. 3. Change in air volume and impedance during respiration. In the lower part of the figure a proper amount of the air volume signal is electrically subtracted from the impedance signal to eliminate in the impedance the direct effect of air volume variation between expiratory E and inspiratory I level.

Table 1 Clinical data. Early-clamped infants.

No	Case	Sex	Gest age weeks	Birth weight g	Hb g % at hrs	Haematocrit t hrs	Mother condition
I	V	f	4	4 100	16 5	50	Good
II	Hu	f	41	3 540	1_0	39	Good
III	W	m	39	710	15 9	53	Good
IV	Ja	m	41	4 000	14 8	50	Good
V	Jo	m	39	_100	16 0	54	Slight t xemia
VI	F	f	4	3,580	15 6	48	Good
VII	Ha	f	41	3 400	16.2	49	Good
Mean			40 0	3 330	15 4	40 0	
S D			1 51	10	1 6	4 9	
				Late-clamped infants			
I	B	m	39	3,300	22.3	4	Good
II	R	m	30	3,540	*0	64	Good
III	S	f	40	3 3*0	22.3	4	Good
IV	K	m	40	3 600	*0.5	65	Good
V	B B	m	40	3 100	19 6	61	Good
VI	U	m	4	3,010	18 9	56	Good
VII	Bj	m	39	3 160	18	50	*Albuminuria*
Mean			39 9	3 300	*0.4	64 7	
S D			1 07	10	1 5	7 0	

was classified as asphyctic They were chosen randomly thus the first baby born after commencement of work in the morning was studied Every other child had early clamping and the others late clamping Early clamping was performed within 10 seconds after birth and before the first breath Late clamping took place after five minutes with the placenta in a position 20 cm above the newborn but without milking of the umbilical cord For further checking of the reliability of the procedure haemoglobin and arterial haematocrit were sampled at two hours of life (43) These and other basic data on the newborn infants are to be found in Table 1

Methods

The instrument used to measure TTI was based on a four electrode constant-current half bridge having a 0.2 mA peak to-peak 50 kHz source The output is directly proportional to the magnitude of the impedance |Z| The apparatus is described earlier in detail (32 33)

All babies were studied in the supine position with one pair of electrodes placed immediately below the right clavicle in the mid-clavicular line the other pair on the back of the right thoracic half about two cm below the caudal margin of the scapula These positions were chosen to make the electrical field cover as much pulmonary tissue as possible with a minimal influence of mediastinal and other extrapulmonary structures The electrodes were removed after each study

ECG was recorded through separate snap-on electrodes with leads from the extremities

Mechanics of respiration (lung compliance) was calculated from tidal volumes measured with a reverse plethysmograph as described by Karlberg *et al* (10) and oesophageal pressure changes recorded through a saline filled, open, polyethylene catheter in the distal third of the oesophagus, connected to a pressure transducer

Signals from the impedance apparatus ECG reverse plethysmograph and oesophageal catheter transducers were simultaneously recorded by an ink jet recorder and also reproduced on a four channel oscilloscope

Table 14. [illegible]

Case no.	Age at study	Heart rate	Resp rat	Tidal volume V_T	Pressure diff at no flow P_T	Compliance per kilogram C/kg	Impedance at expiratory level $\|Z_e\|$	Inter electrode distance a	$\|Z_e\|/a$	Tidal impedance $\|Z_T\|$	$\|Z_T\|/V_T$	$\frac{\|Z_T\|}{\|Z_e\|V_T}$	$\|Z\|$	$\frac{\|Z\|}{\|Z_T\|}$
	hrs	per min	per min	ml	cmH$_2$O	$\frac{ml}{cmH_2O\ kg}$	Ω	cm	$\frac{Ω}{cm}$	Ω	$\frac{Ω}{ml}$	$\frac{\%}{ml}$	Ω	%
Lat I	2	140	48	22.3	6.07	1.01	40.5	10	4.05	1.10	.054	.132	.363	34
	6	110	61	22.5	4.93	1.35	38.0		3.80	.68	.030	.055	.096	10
	12	112	59	23.7	5.96	1.21	50.5		5.05	1.08	.046	.084	.249	23
	24	106	67	23.8	4.34	1.72	48.5		4.85	76	.031	.067	.033	3
II	2	130	114	18.0	5.76	.74	46.2	11	4.20	.39	.026	.044	.060	15
	6	115	82	18.8	4.61	1.16	52.3		4.75	47	.026	.049	.081	17
	12	142	86	28.8	4.98	1.48	50.5		4.63	42	.017	.033	.171	40
	24	100	65	23.0	4.92	1.33	48.6		4.84	45	.020	.041	.004	1
III	2	123	28	14.4	7.88	.55	34.4	10	3.44	.60	.045	.134	.470	71
	6	110	25	18.6	8.82	.64	44.3		4.43	77	.041	.094	.265	34
	12	128	31	23.6	8.40	.84	45.9		4.59	78	.032	.069	.230	30
	24	120	47	31.9	9.17	1.08	38.6		3.86	93	.029	.075	.254	38
IV	2	128	71	16.6	4.80	.92	43.0	12	3.58	79	.060	.116	.350	31
	6	128	8	15.6	6.37	.71	45.1		3.81	.86	.056	.134	.041	48
	12	130	69	14.7	4.28	.96	46.9		3.83	.54	.036	.079	.009	5
	24	126	79	16.1	4.40	1.00	50.5		4.21	.53	.033	.044	.036	7
V	2	105	54	10.6	7.7	.44	30.0	9.5	3.16	.46	.044	.145	.090	21
	6	98	34	16.4	7.9	.85	38.0		4.00	.64	.039	.103	.257	40
	12	106	45	23.6	8.8	.78	51.0		5.37	1.07	.045	.068	.373	26
	24	112	84	29.9	10.1	.93	42.0		4.42	4	.094	.040	.103	13
VI	2	142	60	30.5	9.5	1.09	44.0	11	4.91	1.93	.063	.075	.285	15
	6	118	71	41.3	8.8	1.42	49.0		4.45	1.63	.040	.063	.101	8
	12	125	60	35.5	8.0	1.48	49.5		4.50	2.56	.072	.066	−.031	−1
	24	98	73	57.9	11.0	1.75	49.5		4.50	3.15	.055	.110	−.030	−1
VII	2	137	80	17.7			39.0	10	3.90	.63	.036	.092	.137	22
	6	120	40	18.5			47.0		4.70	78	.042	.090	.098	12
	12	115	50	18.7			26.0		2.60	77	.046	.128	.046	8
	24	118	40	26.7			24.0		2.40	1.09	.041	.123	.058	8

Table 2 Primary and calculated values from ea ly lamped infants (ECI)

Case no	Age t study	Heart rat	Resp rate	Tidal volume V_T	Pressure diff at no fl w P_T	Compliance per kilogram $\frac{C}{kg}$	Impedance at xpiratory level $\|Z_e\|$	Int r electrode distance a	$\frac{\|Z_e\|}{a}$	Tidal impedance $\|Z_T\|$	$\frac{\|Z_T\|}{V_T}$	$\frac{\|Z_T\|}{\|Z_e\|V_T}$	$\|Z_d\|$	$\frac{\|Z_d\|}{\|Z_T\|}$
	hrs	per min	per min	ml	cmH O	$\frac{ml}{cmH_2O\ kg}$	Ω	cm	$\frac{Ω}{cm}$	Ω	$\frac{Ω}{ml}$	$\frac{\%}{ml}$	Ω	%
Early I	2	125	65	14 4	6 94	.51	4..1	13	3..4	65	015	107	000	15
	6	136	50	15 2	5 44	68	48 1		3.70	.51	033	070	I I	24
	12	142	57	19.5	6 80	70	52 0		4 07	.53	027	051	15	*0
	24	148	74	19 0	4 1	1 13	50 8		3 80	.45	0*4	045	057	13
II	2	112	44	38.5	8 47	1..0	57 0	1	4 82	1 11	0*9	050	111	10
	6	132	47	31 9	7.84	1 16	51 0		4.32	80	0*8	053	100	11
	12	120	47	*0 1	7 00	1 05	53 0		4 4	67	023	044	095	14
	24	140	56	39 0	8 08	1.37	55 4		4 0..	60	017	031	115	17
III	2	110	46	15 2	3 75	1.50	47 0	10	4 *9	17	031	064	159	34
	6	133	00	16.2	5.49	1 09	38 4		3 84	03	030	101	.23	37
	12	162	62	10 2	4 56	1 32	45 0		4 50	.50	034	076	2*0	41
	24	130	52	25.8	6 54	1 40	42 0		4.20	72	02*	060	060	8
IV	2	135	78	24 8	8 60	72	56.5	13	4.35	41	017	030	— 0*4	0
	6	130	78	28.3	8 71	81	53.5		4.27	52	018	033	040	10
	12	125	84	31 7	8 84	90	53 4		4 11	48	015	028	138	29
	24	130	60	27.5	6 72	1 02	57 0		4 45	10	015	025	075	10
V	2	125	66	22.5	7 76	1 38	41.2	0	4.58	75	033	080	0*0	3
	6	118	60	30.5	10 13	1 43	60 7		6 74	77	025	012	013	2
	12	110	52	28 3	8 02	1 51	61 1		6 79	70	028	015	009	1
	24	112	49	16 8	5 00	1 60	47.5		5.28	57	034	072	013	2
VI	2	132	64	30 2	8 62	97	51 1	0	5 08	33	011	021	101	49
	6	138	41	42 6	9 65	1.25	58 1		6 46	34	008	014	026	8
	12	145	64	41.2	9.80	1 18	50 6		5 62	71	017	034	057	0
	24	155	68	36.2	7 47	1.30	58.3		6 48	31	000	015	034	11
VII	2	152	67	20 0	0 67	91	38 7	10	3 87	.32	010	012	117	35
	0	150	53	21 9	6 00	95	37 1		3 71	62	028	077	115	23
	l	150	53	16 0	0 20	76	5* 0		5 00	.31	10	[illegible]	1?1	0
	24	128	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 2. Group means and t values for group differences for compliance and impedance variables.

	h	C/kg, ml/cmH₂O kg Mean	S.D	t	X_s, Ω Mean	S.D	t	$\lvert X_s\rvert$, Ω/cm Mean	S.D	t	$\lvert Z_T\rvert / V_T$, Ω/ml Mean	S.D	t	$\lvert Z_T\rvert / V_T\lvert X_s\rvert$, %/ml Mean	S.D	t	$\lvert Z\rvert$, Ω Mean	S.D	t	$\lvert Z\rvert/\lvert Z_T\rvert$, % Mean	S.D	t
RCI	2	1.04	.36		47.9	7.6		4.48	.77		.026	.012		.056	.030		.086	.077		19	21	
	6	1.06	.36		50.0	9.3		4.72	1.31		.026	.010		.064	.029		.094	.062		10	13	
	12	1.06	.30		52.3	4.9		4.93	.93		.022	.007		.046	.016		.114	.070		23	16	
	24	1.25	.29		51.0	6.4		4.78	.86		.022	.009		.045	.021		.093	.109		16	16	
Diff	24-2	.21	.27	1.19	3.1	5.5	.83	.30	.64	.70	−.004	.010	.76	−.013	.025	.84	.007	.116	.16	−3	22	.31
LCI	2	.79	.26		41.0	7.8		3.99	.68		.046	.013		.107	.033		.236	.161		30	20	
	6	.99	.26		46.8	5.9		4.48	.63		.039	.010		.067	.029		.134	.089		24	16	
	12	1.13	.31		47.1	5.4		4.51	.63		.042	.017		.062	.026		.124	.126		18	16	
	24	1.30	.26		44.3	5.5		4.31	.37		.033	.012		.077	.029		.088	.102		7	14	
Diff	24-2	.52	.23	2.77	3.3	5.9	.89	.32	.57	1.24	−.012	.010	1.94	−.030	.048	1.78	−.150	.129	2.50	−22	12	2.41
RCI LCI	2			1.39			1.67			1.60			3.04			3.00			2.36			.95
	24			.24			2.13			1.60			3.09			2.40			.63			1.12
Diff	24-2			2.36			.04			0.06			1.55			.99			2.66			2.03

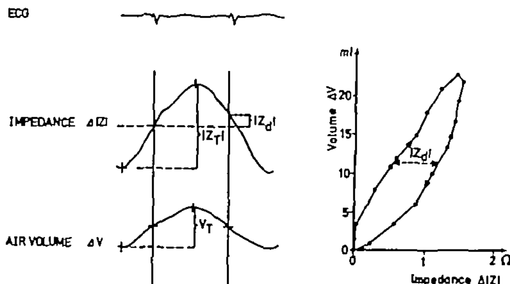


Fig 4 Analysis of a breath. Points of mid inspiratory and mid-expiratory volume on the air volume curve are w th perpendicular l nes ma ked off on the impedance curve The difference in level between the t o points on the impedance curve called $|Z_d|$ In the right part of the f gure the same breath is presented in the form of resp ratory loop from hange in ai olume and impedance The interrupted line t mid a volume is a represent tion of $|Z_d|$

volume curve and then draw a horizontal line to the corresponding point in expiration, i e between points of equal volumes These two points were marked off on the impedance curve through perpendicular lines The difference in level between impedance at mid inspiration and mid expiration was measured and called $|Z_d|$ (Fig 4) This variable is normalized in the calculations with respect to $|Z_T|$ with the aim of eliminating the direct influence of the size of the breath

Procedure

The babies were examined at the age of 2 6 12 and 24 hours Calculations were made each time on five breaths from records with stable baseline (i e <1 mm deviation in end expiratory level) for the three variables impedance air volume and oesophageal pressure A mean was taken for these breaths mainly to minimize the effects of cardiac activity on the impedance and oesophageal pressure curves (44) With the electrode position used, the effect from one cardiac systole on the impedance was always less than three per cent of $|Z_T|$

Numerical primary and calculated values from the studies are grouped together in Table 2

Statistical analyses

Mean values and standard deviations of all variables were calculated and plotted with 95 per cent confidence intervals as obtained with the Wilcoxon test (25) Differences between the two groups were tested with standard t test individually for each time Significant differences were tested with the Wilcoxon rank test as well to ensure that no unfavourable influence of the distribution existed

The differences in the respective groups between values measured at 2 and 24 hours were tested in the same way as well as with the Wilcoxon signed rank test to find out whether or not the mean of these differed from zero. Furthermore a trend analysis with sign test was performed using all differences together i e. for 2–6 2–12 and 2–24 hours.

In the text all significances refer to the 95 per cent level unless otherwise specified

To reveal possible relationships between the time dependent changes in the variables of the individual or between the two groups, the regression lines for some variables were calculated against age given in logarithmic values as this led to a more rectilinear relationship than with arithmetic age

Table 4. Slope values for individual regression lines.

Case no.	$\frac{C/kg}{\log t}$	$\frac{\lvert Z_0\rvert}{\log t}$	$\frac{\lvert Z_0\rvert/a}{\log t}$	$\frac{\lvert Z_T\rvert/V_T}{\log t}$	$\frac{\lvert Z_T\rvert/(V_T\lvert Z_0\rvert)}{\log t}$	$\frac{\lvert Z_d\rvert}{\log t}$	$\frac{\lvert Z_d\rvert/\lvert Z_T\rvert}{\log t}$
ECI I	0.51	8 9	0.65	−0 019	−0 060	−0 02	1
II	0.01	−2.4	−0.20	−0.011	−0.017	0 00	7
III	−0.02	3.8	−0.39	−0.003	−0.001	−0.07	19
IV	0.27	0 2	0.03	−0.002	−0.005	0.12	27
V	0.20	7 7	0.84	0.001	−0.011	−0.01	1
VI	0.35	4.3	0 45	0.001	0.000	−0.11	36
VII	−0.14	8 0	0.90	0.007	0.006	0 16	14
LCI I	0 65	8.3	0 83	−0.017	−0.062	−0 28	24
II	0.42	0.7	0 07	−0.007	−0.012	−0 04	3
III	0.47	6 2	0.52	0.017	−0.069	−0 21	34
IV	0 12	6 9	0.58	−0.019	−0 053	−0.27	42
V	0 45	14 4	1.52	0.014	0.077	−0.03	8
VI	0.85	−4 1	−0.37	0.000	0.030	−0.31	16
VII	—	−4.8	−0.46	0 006	0 036	−0 08	14

Possible interrelationships between changes in the variables were first analysed graphically by plotting the slopes of the individual cases against each other (Table 4 Fig 6) When relationships were probable further sign tests were performed on the quotients of all differences in each group.

Results

The two groups of babies are differentiated by the haematocrit and haemoglobin values t two hours of age These differences are st tistically highly significant (p>99.5)

No difference existed between the ECI and the LCI w th regard to gest tional age and birth weight

Mean values M standard deviations S D and t test results for the variables are found in T ble 3 In Fig. 5a–f are collected means and 95 per cent confidence limits for the same variables at all times studied.

The absolut value of basic impedance Z_0 and this value corrected for interelectrode transthoracic distance Z_0 / (Fig 5b), behave in a qualit tively similar manner an increase is noted in LCI from * to 1 hours, with a decreasing tendency from 1 t 4 hours. ECI have no significant variations in those variables though mean values follow the same pattern as just described N significant difference in mean $|Z_0$ is noted between ECI and LCI but LCI are numerically lower during the whole time of the study

The impedance change per unit air volume change normalized in relation to $|Z_0|$ i e $|Z_T|/(V |Z_0|)$ was found to be significantly more pronounced for the late-clamped group at all times (Fig 5d) This is also the case for $|Z_T|/V_T$ (Fig 5c) LCI show a drop in $|Z_T|/V_T$ as assessed from the values at ° and 24 hours. By the use of the sign test a drop is also noted in $|Z_T|/(V_T |Z_0|)$

The looped relationship between ΔV and Δ Z| expressed as the difference in level on the impedance curve between the inspiratory and expiratory slopes at mid-inspiratory volume |Z | is significantly higher at two hours after late clamping No difference between LCI and ECI is found at °4 hours. These facts are also reflected in a significant drop in $|Z_d|$ from to °4 hours in LCI but not in ECI (Fig 5e).

On normalizing in respect t tidal impedance a somewhat different picture is obtained $|Z_d|/|Z_T|$ does not differ between the two groups at two hours though a significant decline is obvious

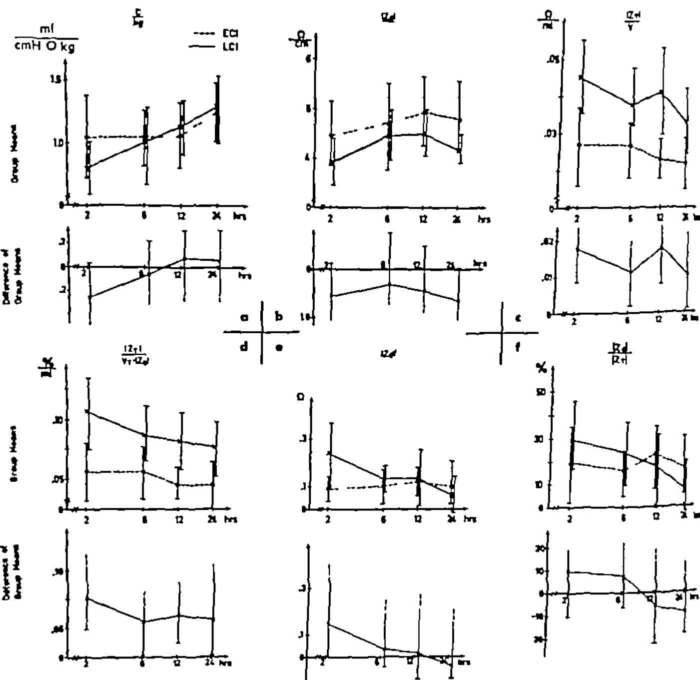


Fig 5 Complia ice an l mpedance variables from 2 to 4 hours. Group means are presented with two-sided 95 per cent confidence intervals and bel w diff rences between group means (ECI–LCI) with one-sided 95 per cent confidence intervals. For deta ls, see text

Table 4. Slope values for individual regression lines.

Case no.	$\frac{C/kg}{\log t}$	$\frac{\lvert Z_0\rvert}{\log t}$	$\frac{\lvert Z_0\rvert/a}{\log t}$	$\frac{\lvert Z_T\rvert/V_T}{\log t}$	$\frac{\lvert Z_T\rvert/(V_T\lvert Z_0\rvert)}{\log t}$	$\frac{\lvert Z_d\rvert}{\log t}$	$\frac{\lvert Z_d\rvert/\lvert Z_T\rvert}{\log t}$
ECI I	0.31	3.9	0.64	−0.019	−0.049	−0.02	1
II	0.01	−2.4	−0.20	−0.011	−0.017	0.00	7
III	−0.02	−3.9	−0.39	−0.003	−0.001	−0.07	19
IV	0.27	0.2	0.02	−0.002	−0.006	0.12	27
V	0.20	7.7	0.86	0.001	−0.011	−0.01	1
VI	0.25	4.3	0.48	0.001	0.000	−0.11	26
VII	−0.16	9.0	0.90	0.007	0.006	0.16	14
LCI I	0.64	3.2	0.53	−0.017	−0.042	−0.25	24
II	0.02	0.7	0.07	−0.007	−0.012	−0.04	3
III	0.47	4.2	0.42	0.017	−0.050	−0.21	34
IV	0.12	5.9	0.59	−0.019	−0.043	−0.27	42
V	0.45	14.4	1.42	0.014	0.077	−0.02	8
VI	0.68	−4.1	−0.37	0.000	0.030	−0.31	16
VII	—	−4.6	−0.46	0.006	0.036	−0.06	14

Possible interrelationships between changes in the variables were first analysed graphically by plotting the slopes of the individual cases against each other (Table 4, Fig. 6). When relationships were probable, further sign tests were performed on the quotients of all differences in each group.

Results

The two groups of babies are differentiated by the haematocrit and haemoglobin values at two hours of age. These differences are statistically highly significant ($p > 99.5\%$).

No difference existed between the ECI and the LCI with regard to gestational age and birth weight.

Mean values M, standard deviations S.D. and t test results for the variables are found in Table 3. In Fig. 5a–f are collected means and 95 per cent confidence limits for the same variables at all times studied.

The absolute value of basic impedance $|Z_0|$ and this value corrected for interelectrode transthoracic distance Z_0/a (Fig. 5b), behave in a qualitatively similar manner: an increase is noted in LCI from 2 to 6 hours with a decreasing tendency from 12 to 24 hours. ECI have no significant variations in those variables though mean values follow the same pattern as just described. No significant difference in mean $|Z_0|$ is noted between ECI and LCI but LCI are numerically lower during the whole time of the study.

The impedance change per unit air volume change, normalized in relation to $|Z_0|$, i.e. $|Z_T|/(V_T |Z_0|)$ was found to be significantly more pronounced for the late-clamped group at all times (Fig. 5d). This is also the case for $|Z_T|/V_T$ (Fig. 5c). LCI show a drop in $|Z_T|/V_T$ as assessed from the values at 2 and 24 hours. By the use of the sign test a drop is also noted in $|Z_T|/(V_T |Z_0|)$.

The looped relationship between ΔV and $\Delta|Z|$ expressed as the difference in level on the impedance curve between the inspiratory and expiratory slopes at mid-inspiratory volume $|Z_d|$ is significantly higher at two hours after late clamping. No difference between LCI and ECI is found at 24 hours. These facts are also reflected in a significant drop in $|Z_d|$ from 2 to 24 hours in LCI but not in ECI (Fig. 5e).

On normalizing in respect to tidal impedance a somewhat different picture is obtained. $|Z_d|/|Z_T|$ does not differ between the two groups at two hours though a significant decline is obvious

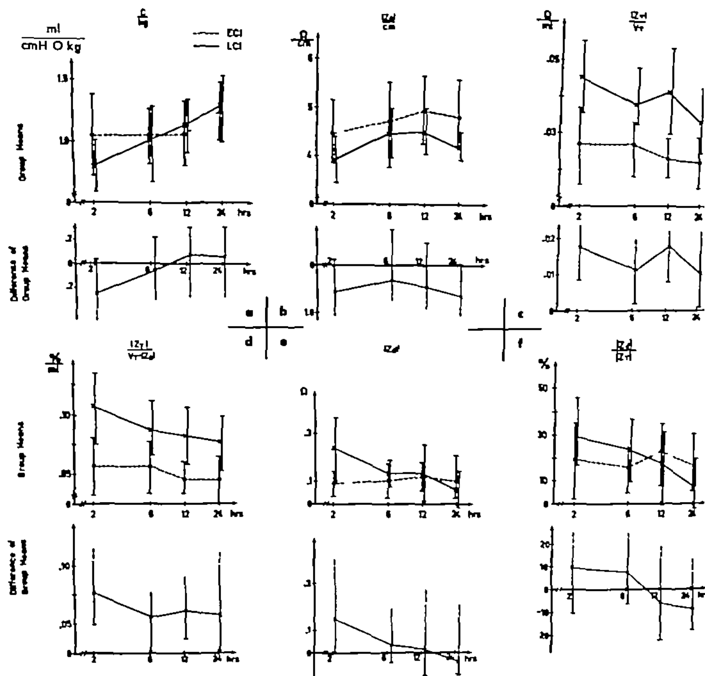


Fig 5 Compliance and impedance variables from to 24 hours. Group means are presented with two-sided 95 per cent confidence intervals nd below differences between group means (ECI–LCI) with one-sided 95 per cent confidence intervals. For details, see text.

Table 4. Slope values for individual regression lines.

Case no.	$\frac{C/kg}{\log t}$	$\frac{\lvert Z_o\rvert}{\log t}$	$\frac{\lvert Z_o\rvert/a}{\log t}$	$\frac{\lvert Z_T\rvert/V}{\log t}$	$\frac{\lvert Z_T\rvert/(V_T \lvert Z_o\rvert)}{\log t}$	$\frac{\lvert Z_d\rvert}{\log t}$	$\frac{\lvert Z_d\rvert/\lvert Z_T\rvert}{\log t}$
ECI I	0.51	6.9	0.05	−0.019	−0.040	−0.02	1
II	0.01	−2.4	−0.20	−0.011	−0.017	0.00	7
III	−0.02	−3.9	−0.29	−0.003	−0.001	−0.07	19
IV	0.27	0.3	0.02	−0.002	−0.004	0.12	27
V	0.20	7.7	0.34	0.001	−0.011	−0.01	1
VI	0.35	4.3	0.48	0.001	0.000	−0.11	36
VII	−0.16	9.0	0.90	0.007	0.006	0.16	14
LCI I	0.65	5.3	0.53	−0.017	−0.052	−0.25	24
II	0.62	0.7	0.07	−0.007	−0.012	−0.04	3
III	0.47	6.2	0.62	0.017	−0.069	−0.21	34
IV	0.12	6.9	0.66	−0.019	−0.033	−0.27	42
V	0.45	14.4	1.52	0.014	0.077	−0.03	5
VI	0.54	−4.1	−0.27	0.000	0.030	−0.31	16
VII		−4.6	−0.46	0.004	0.036	−0.04	14

Possible interrelationships between changes in the variables were first analysed graphically by plotting the slopes of the individual cases against each other (Table 4 Fig 6). When relationships were probable further sign tests were performed on the quotients of all differences in each group.

Results

The two groups of babies were differentiated by the haematocrit and haemoglobin values at two hours of age. These differences are statistically highly significant ($p > 99.5\%$).

No difference existed between the ECI and the LCI with regard to gestational age and birth weight.

Mean values M standard deviations S D and t test results for the variables are found in Table 3. In Fig. 5a–f are collected means and 95 per cent confidence limits for the same variables at all times studied.

The absolute value of basic impedance Z_o and this value corrected for interelectrode transthoracic distance Z_o/a (Fig. 5b), behave in qualitatively similar manner: an increase is noted in LCI from 2 to 12 hours, with a decreasing tendency from 12 to 24 hours. ECI have no significant variations in those variables though mean values follow the same pattern as just described. No significant difference in mean $|Z_o|$ is noted between ECI and LCI but LCI are numerically lower during the whole time of the study.

The impedance change per unit air volume change normalized in relation to $|Z_o|$ i.e. $|Z_T|/(V_T\,|Z_o|)$ was found to be significantly more pronounced for the late-clamped group at all times (Fig 5d). This is also the case for $|Z_T|/V_T$ (Fig 5c). LCI show a drop in $|Z_T|/V_T$ as assessed from the values at 2 and 24 hours. By the use of the sign test a drop is also noted in $|Z_T|/(V_T\,|Z_o|)$.

The looped relationship between ΔV and $\Delta|Z|$ expressed as the difference in level on the impedance curve between the inspiratory and expiratory slopes at mid-inspiratory volume $|Z_d|$ is significantly higher at two hours after late clamping. No difference between LCI and ECI is found at 24 hours. These facts are also reflected in a significant drop in $|Z_d|$ from 2 to 24 hours in LCI but not in ECI (Fig 5e).

On normalizing in respect to tidal impedance a somewhat different picture is obtained. $|Z_d|/|Z_T|$ does not differ between the two groups at two hours though a significant decline is obvious

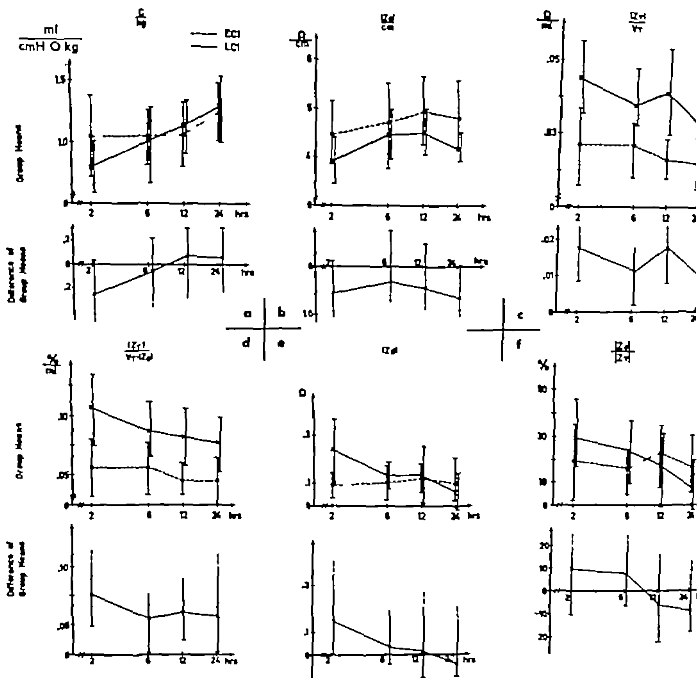


Fig 5 Compliance nd impedance variables from to 4 hours. Group means are presented with two-sided per cent confidence intervals nd, below d fferences between group means (ECI–LCI) with one-sided 95 per cent conf dence intervals. For details, see t t

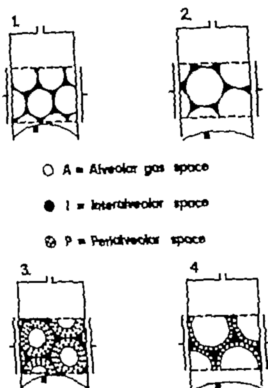


Fig 7 Schematic lung model with bilaterally applied impedance electrodes and marking of the lung parenchyma covered by the electric field. On the assumption of constant volume of the electric field no change in impedance takes place on inspiration with densely packed spheres (1 2). With the existence of perialveolar space the relative increase of alveolar space is larger causing an increase in impedance with inspiration (3–4).

in LCI from to 24 hours (Fig 5f) No such drop is noted in ECI

Lung compliance was measured in seven ECI and six LCI in one case of the last group oesophageal pressure readings were not obtained for technical reasons A tendency towards increasing compliance is seen in our material (Fig 5a) In tests limited to the difference between and 4 hours this rise was significant for the late clamped group corresponding to an increase in tidal volume

The regression lines for some variables are calculated for the individual case and the slopes (b in the regression equation $y = a + b \log t$) are grouped together in Table 4

In our comparative analyses between compliance and the impedance variables, an inverse correlation with $|Z_T|/(V_T|Z_a|)$ is revealed in Fig 6c. This correlation is significant for both groups of infants when checked with a sign test.

The same tendency is found when the comparison is made merely with $|Z_T|/V_T$ (Fig 6b) and also a positive correlation is noted with $|Z_a|$ proper (Fig. 6a)

The slopes for the variable $|Z_a|/|Z_T|$ have also been analysed versus compliance slopes. In all late clamped cases a negative correlation is found while the situation for ECI is inconclusive (Fig 6c) If, on the other hand, the comparison is made not with $|Z_a|/|Z_T|$ but with $|Z_a|$ a negative correlation appears also for ECI (Fig 6d).

Discussion

Transthoracic impedance is directly correlated with air volume changes in the lungs during respiration (2, 13 44) According to our earlier reports TTI is furthermore a function of pulmonary fluid volume (21 34 44) Measurements of pulmonary functional residual capacity FRC by other workers (16, 22 39) have shown that in the newborn with uneventful neonatal adaptation FRC is essentially constant or increases only slightly from about one hour to 4–7 days of life. Comparison between ECI and LCI has however shown a delay of the pulmonary aeration in LCI with a lower FRC during the first six hours after birth (31)

The initial air filling of the lungs provokes a resorption of bronchial and alveolar fluid t the capillaries and interstitial space. This resorption as studied in newborn animals causes an expansion of the interstitium during the first half hour after which time a gradual shrinkage of the interstitial space takes place concomitant with a large lymph drainage out of the lungs and a falling total pulmonary water content (3 1., 18 35 40). This successive decrease of the expanded interstitial space is estimated to continue for about six hours after birth.

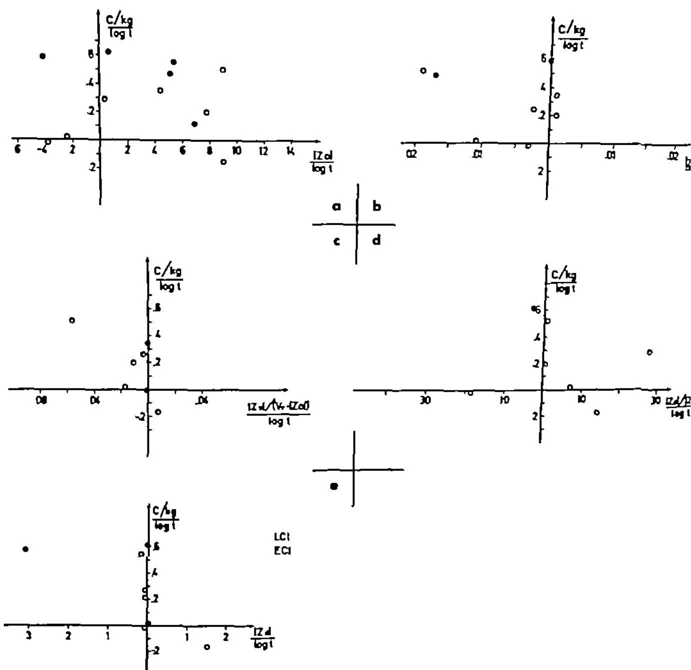


Fig. 6. Slopes of regression lines fo different impedance variables versus compliance for the individual cases. For details, see text.

and LCI and cannot be used to explain the difference between the groups.

Evidently other mechanisms have also to be considered for the variation of pulmonary blood volume with respiration. Our previously described model of pulmonary air/fluid relationship offers another explanation of relative volume variations in the lungs (34). From a geometrical point of view increase of alveolar size in inspiration also increases total pulmonary interalveolar space as schematically depicted in Fig. This space has to be filled with movable substance (blood lymph or interstitial fluid) originating either from the so called perialveolar space if available or from outside the lungs, mainly through the pulmonary arteries or veins (by decrease in outflow from the lungs or even reversed flow) An increase of pulmonary blood volume due to this geometrical effect is present both when the inspiration is induced by negative and positive pressure

With relatively more blood in the lungs at end-expiratory level, which seems reasonable in LCI as compared with ECI less blood is needed from outside the lung to fill the increasing interalveolar space during inspiration and the ratio $Z_T/(V \cdot |Z_e|)$ is accordingly larger This hypothesis is supported by the drop in this ratio from 2 to 24 hours in LCI concomitant with a decreasing total blood volume and a decreasing left right shunt through ductus arteriosus indicating a falling pulmonary blood vol me

The looped shape for the relation of air volume to impedance change during breath as represented by the variable Z_4 is a sign of a discrepancy between air and blood flow in and out of the lungs, most pronounced in early piration. In relativ terms more blood than air leaves the lungs in the beginning of xpiration. With large pulmonary blood volume t end-expiratory level redistribution of blood within the lung can satisfy the need created by the geometrical factor and the blood volume entering the lungs due to the suctioning effect i available to leave the lung immediately when the negative pressure is released. $|Z_4|$ is high in LCI at two hours and decreases during the time of study This indicates that more blood than geometrically necessary is suctioned into the lungs with inspiration, most pronounced in the beginning of the study

No change with time is noted in $|Z_4|$ for ECI.

The correlations between changes in the various impedance variables and compliance demonstrate possible concomitant variations. As previously described (31) and also indicated by our studies lung compliance increases during the first day of life, more definitely for LCI

From the results of the correlations it appears that there are quantitative simultaneous changes with time in the impedance variables and compliance in the individual cases as well as between the two groups of infants An increase in compliance is accompanied by changes in the impedance variables that are interpreted above as depending on increasing shift of blood in and out of the lungs with respiration and increasing ratio air/fluid inside the lungs.

Two possibilities appear for an explanation linking together these changes in the neonate between * and 24 hours of life, i.e. increasing FRC and/or decreasing pulmonary fluid volume, with the changes most pronounced in LCI

The main aeration of the lungs is completed at two hours of age but mechanics of breathing continue to change after this time with an increase in lung compliance for several days, especially for LCI (5 8 20, 31) Koch (23) states that the increase in compliance during the first day of life is accompanied by a similar but proportionately smaller increase in FRC indicating an effect on lung compliance that is not directly related to FRC.

As pointed out the total blood volume in LCI is estimated to drop about 10 per cent on average during the time of our study The impedance results indicate that this drop is also reflected in a reduction of pulmonary blood volume with an effect on pulmonary mechanics Variations in pulmonary blood volume could thus explain a difference in the courses for compliance and FRC.

The total blood volume in LCI is about 25 per cent above that of ECI at the commencement of our study at two hours as judged from the haemoglobin and haematocrit values According to Usher et al (43) who found essentially the same value at two hours this difference drops to around 10 per cent at 24 hours of age The drop is almost exclusively due to a loss of plasma in LCI If a significant part of this plasma transudation occurs in the lungs of LCI the added extra fluid in the interstitial space may interfere with and prolong the process of shrinking just described

Pulmonary blood volume is dependent on inter alia total blood volume (21) Variations in pulmonary blood flow caused by changes in pulmonary vascular resistance also affect pulmonary blood volume and hence TTI and have to be considered in this discussion. There is a large increase in the pulmonary blood flow during the first two hours after birth especially marked during the first half hour The flow reaches its maximum some time between two and six hours corresponding to the first part of the present study when the initial right left shunt through ductus arteriosus and foramen ovale has ceased and the increase of the left right shunt through ductus arteriosus has levelled off (1 7 11 26) The lungs are thus perfused by the ductal flow in addition to the entire right cardiac output The gradual constriction of ductus arteriosus after 3–6 hours reduces the flow and a functional closure prevails some time during the latter part of the first day of life (15 38 45)

Basic transthoracic impedance $|Z_0|$ is influenced by the described changes in the various volume fractions changes that have partly counteracting effects on the impedance The numerically lower $|Z_0|$ for LCI during the whole study is in accordance with the higher total blood volume in these infants than in ECI The increase in $|Z_0|$ from 2 to 12 hours is partly an effect of the decrease in total and thus pulmonary blood volume most pronounced in LCI as a result of a delayed adaptation in this group Besides the decreasing pulmonary blood volume the shrinkage of inter space and a possible increase of FRC al to increase $|Z_0|$ The possible fall in $|Z_0|$ 12 to 24 hours coincides with an incre total blood volume reported for this by Usher et al (43)

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Summary

Transthoracic impedance TTI in combination with recordings of air volume change and oesophageal pressure has been used to analyze time dependent variations in the ratio air/fluid *during the first day of life* as well as the dynamic interrelationship between air and fluid in the lungs during *respiration*

Two groups of infants seven with early and seven with late clamping of the umbilical cord were studied at 2 6 12 and 24 hours of age *These groups are known to have a dif* ference in total blood volume decreasing during the time of study

Especially in late-clamped infants characteristic changes in impedance variables are noted Basic transthoracic impedance $|Z_0|$ reflecting the static ratio air/fluid is initially low and increases till 12 hours of age a net result of a decrease in pulmonary blood volume *interstitial fluid* and *possibly some* contribution from an increase in pulmonary air volume *A tendency towards a fall in* $|Z_0|$ *from 12 to* 24 hours coincides with an enlargement of the total blood volume

Variations between early and late-clamped infants are larger for the dynamic impedance variables than for $|Z_0|$ The ratio $|Z_T|/V_T$ of impedance variation per unit air volume change during respiration is higher *for late* clamped infants during the whole study though *decreasing with time This implies* that these infants have a larger amount of *fluid in the lungs as compared with early* clamped infants also decreasing with time In accordance with the presented physical model for volume relations in the lungs the amount of blood that needs to be moved into the lungs with inspiration is relatively smaller when the pulmonary blood volume is higher

A looped relation between air *volume change* and impedance change during a breath $|Z_d|$ is most *pronounced in* late-clamped infants at the commencement of the study *significantly decreasing* with time The existence of a $|Z_d|$ means that a larger blood volume than necessary for the geometrical requirements has ente the lungs during inspiration, a volume tha allowed to leave in early expiration. prerequisite of a high $|Z_d|$ is a large pulmon *blood volume* For infants with early clamp of the umbilical cord no significant variab *are noted in the impedance variables*

It is concluded that late-clamped infa *compared to early clamped infants in addit* to their larger total blood volume also hav larger pulmonary *fluid volume the increm* mainly consisting of blood A correlation found between change in lung complia and the impedance variables especially c cerning the late-clamped group and a suggest is made that lung compliance varies invers with the pulmonary fluid volume

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Pulmonary fluid and air volumes as studied with transthoracic impedance measurements — general discussion and summary

In this section the main results of Parts I–V are first surveyed, followed by a general discussion integrating the findings with available physiologic knowledge concerning the perinatal period.

Results

Part I

The transthoracic impedance as measured between two diametrically placed electrodes in the sagittal plane is found to be related to the electrode size and the current distribution in the neighbourhood of the electrode can be considered to have spherical symmetry. The potential distribution on the circumference arising from a voltage applied to such electrodes is furthermore found to coincide with the potential distribution found on the circumference of a cylinder filled with a homogeneous electrolyte. The two measured distributions also agree with theoretical calculations. From a macroscopic point of view the thorax can be considered to be a homogeneous conductor and on this basis an equation is derived in which resistance variations are expressed in terms of volume variations

$$\frac{\Delta R}{R} = \frac{V_A}{V_A + V_E}\left(\frac{\Delta V}{V} - \frac{\Delta V_E}{V_E}\right) \qquad (6)$$

This equation can also be used for transthoracic impedance variations as the reactive part of the impedance is small and hence the magnitude of the impedance is approximately equal to the resistive part. I

$$\frac{\Delta R}{R} \approx \frac{\Delta Z}{Z} \qquad (7)$$

The relation, however is derived on the assumption that nonconducting volumes and conducting volumes are independent. In order to be able to include interrelationships between the volumes, we have also developed a model for which qualitative predictions are possible

The instruments used for the measurements are based on a constant-current half bridge using four-electrode technique. The voltage across the measuring electrodes is compared with the voltage across a reference resistor. The same current flows through the reference resistor and the subject. The output of the instrument is a signal proportional to the magnitude of the impedance or the resistive part of the impedance, depending on the detector used.

The difference between magnitude and resistive part is neglected, as the phase-angle is small.

One injection electrode and one measuring electrode are combined in a PVC-housing to an electrode pair with two-cm spacing. The silver discs forming the electrodes are kept at one mm distance from th skin. The space is filled with electrode paste.

The bridge is constructed to have negligibly low sensitivity to leakage currents and unbalance in contact impedances.

Part II

A linear relationship between relative changes in transthoracic impedance and pulmonary blood volume was found in anaesthetized cats. Variations in pulmonary air as well as blood volume induced in several different ways caused impedance variations in accordance with the theoretical expression Eq. 6. Quantitative calculations were relevant in that reasonable values for FRC were obtained

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Pulmonary fluid and air volumes as studied with transthoracic impedance measurements — general discussion and summary

In this section the main results of Parts I–V are first surveyed, followed by a general discussion integrating the findings with available physiologic knowledge concerning the perinatal period.

Results

Part I

The transthoracic impedance as measured between two diametrically placed electrodes in the sagittal plane is found to be related to the electrode size and the current distribution in the neighbourhood of the electrode can be considered to have spherical symmetry. The potential distribution on the circumference arising from a voltage applied to such electrodes is furthermore found to coincide with the potential distribution found on the circumference of a cylinder filled with a homogeneous electrolyte. The two measured distributions also agree with theoretical calculations. From a macroscopic point of view the thorax can be considered to be a homogeneous conductor and on this basis an equation is derived in which resistance variations are expressed in terms of volume variations.

$$\frac{\Delta R}{R} = \frac{V}{V + V}\left(\frac{\Delta V}{V_A} - \frac{\Delta V_E}{V_E}\right) \qquad (6)$$

This equation can also be used for transthoracic impedance variations as the reactive part of the impedance is small and hence the magnitude of the impedance is approximately equal to the resistive part, i.e.

$$\frac{\Delta R}{R} \approx \frac{\Delta Z}{Z} \qquad (7)$$

The relation however is derived on the assumption that nonconducting volumes and conducting volumes are independent. In order to be able to include interrelationships between the volumes, we have also developed a model for which qualitative predictions are possible.

The instruments used for the measurements are based on a constant-current half bridge using four-electrode technique. The voltage across the measuring electrodes is compared with the voltage across a reference resistor. The same current flows through the reference resistor and the subject. The output of the instrument is a signal proportional to the magnitude of the impedance or the resistive part of the impedance depending on the detector used.

The difference between magnitude and resistive part is neglected, as the phase-angle is small.

One injection electrode and one measuring electrode are combined in a PVC-housing to an electrode pair with two-cm spacing. The silver discs forming the electrodes are kept at one mm distance from the skin. The space is filled with electrode paste.

The bridge is constructed to have negligibly low sensitivity to leakage currents and unbalance in contact impedances.

Part II

A linear relationship between relative changes in transthoracic impedance and pulmonary blood volume was found in anaesthetized cats. Variations in pulmonary air as well as blood volume induced in several different ways, caused impedance variations in accordance with the theoretical expression Eq. 6. Quantitative calculations were relevant in that reasonable values for FRC were obtained.

Part III

Valid recordings of TTI require that the electrodes be applied to the skin five minutes before the first reading and that the infants be quiet. Tests of different electrode positions showed that electrodes applied bilaterally to the thorax or obliquely sagittal over the right lung gave the smallest variations among the different infants These two leads also appear to be representative for entire lungs

Hydrostatic effects on the pulmonary fluid and air volumes were revealed by the measurements.

A linear correlation between tidal volume and corresponding impedance variation was confirmed for breaths during quiet respiration. The dynamic relationship between air volume and impedance during a breath was found to include differences between inspiration and expiration.

Part IV

From 15 to 30 minutes of life infants with late clamping LCI and early clamping ECI of the umbilical cord showed a decrease in basic impedance The LCI reached a lower level between 45 and 75 minutes after which time the impedance for this group rises and no statistically significant difference between the two groups remains at two hours The results were applied to a mathematical model from which values at the time of birth were extrapolated backwards.

In a control group of infants, past the period of initial postnatal adaptation, no change in TTI was noted during two hours after application of the electrodes

Part V

Comparison between LCI and ECI during the first day of life reveals differences in impedance variables especially at the commencement of the study when the infants are two hours old LCI have increasing basic impedance show a greater impedance change with respiration and a more pronounced hysteresis in the relation air volume to impedance during a breath as compared with ECI

A change in the lung compliance for th
individual case is correlated with the impedan
variables studied.

Discussion

Electrical background

The influence on the transthoracic *impedan*
of all relevant factors is probably not possib
to elucidate in detail It is however evider
that increasing air volume in a section of th
lung must cause the impedance of this sectio
to rise How much this increase affects th
impedance measured between electrodes on th
surface of the thorax depends on the curren
distribution The results of potential distribu
tion measurements on the surface of cylindrica
models and the human thorax and of impedanc
measurements on the thorax between electrode
of different sizes prove that it is reasonable t
treat the thorax as a homogeneous volume con
ductor It is also reasonable to assume spherica
symmetry to prevail in the current density
distribution near the electrodes.

These findings agree well with the conclusior
of Schwan and Kay (96) who stated that no
gross error exists in the assumption that the
body tissues that conduct the signals recorded
in electrocardiography establish an essentially
homogeneous volume conductor

After experiments in which they excluded different parts of the thorax by insulation, Baker and Geddes (15) concluded that only five per cent of the total current passed through the lungs Their measurements were however performed with the two-electrode technique and their conclusion based on the assumption that a change in impedance is proportional to the current fraction that passed through a section before the insulation When the electrical field is not uniform such an assumption is not correct. To be able to draw conclusions from such measurements it is necessary to estimate the influence of the deformation of the electrical field. This was not done and their statement can thus not be considered a contradiction of our findings and those of others

As noticed by the reader familiar with the TTI technique, the contact impedance of the electrodes is discussed very little in this work. It is instead desired to draw attention to the far more important question of the electrical field just inside the skin. Many investigators include the tissue impedance in the electrode or contact impedance and attribute a large part of the impedance to polarization effects. This is justified only for low frequencies (98). It is easily shown by measurement that the magnitude of the impedance between two electrodes made of silver-discs of one-cm diameter bridged by electrode paste is in the order of a few ohms at 50 kHz. This should be compared with a transthoracic impedance of about 500 ohm measured with the same electrodes.

The principal part of the impedance is thus to be found within the tissue. If the tissue is assumed to be homogeneous as far as concerns the electrical current density the transthoracic impedance measured between two electrodes should be approximately inversely proportional to the electrode diameter. Measurements with electrodes with diameter ranging from 0.6 to 80 mm show that the assumption is reasonable (I). With this result in mind the need for measuring a specific skin impedance proposed by Kinnen (64) appears doubtful. He suggested defining the skin impedance as the portion of the total impedance measured between two equipotential surfaces in contact with the epidermis that is inversely proportional to the electrode area when the internal current flux path is held constant. To measure the skin impedance a technique based on doubling of the electrode area was used and skin admittances per unit area were calculated. The same technique was used by Pasquali (85). In view of the discussion above such a method must be considered questionable as is confirmed by examining the values of Pasquali with respect to electrode diameter (I).

Despite the evidence that polarization effects and skin impedance can be neglected at frequencies of 50 kHz there is an electrode dependence on the impedance that cannot be explained from the true size of the electrode. Part III reports that the impedance measured immediately after the application of the electrodes is higher than the value measured five minutes later even though a four-electrode device is used. This implies that factors exist that affect the current distribution just after applying the electrodes, these can be described in terms of decreasing resistivity in the near vicinity of the electrodes, or of increasing effective electrode area. Which of these two effects is the more important is left for speculation, the existence of electrode dependence must in any case be taken into consideration.

The impedance variation seen when a subject moves, and when pressure is applied to the electrodes, is attributed to the same phenomenon. As matter of fact Hill *et al.* (51) maintain that practically all impedance variations found in impedance plethysmography can be explained by the pressure sensitivity of the electrodes. Slow variations found in the basic impedance that are well correlated to central blood volume can however certainly not be a result of different pressure at the electrodes. Thus the results of Part II to Part V are clear contradictions of the contention that impedance variations in TTI are merely results of variations at the electrodes.

By excluding the near vicinity of the injection electrodes conditions are established permitting one to express differences in TTI in terms of the characteristic impedance. Furthermore the characteristic impedance of a thoracic segment is found to be practically only resistive in agreement with other reported values (85, 97).

This implies that further analyses can be made by considering only the resistivity in the first approximation. An expression derived by Maxwell (74) is used in which the resistivity of a dispersive mixture is expressed in terms of the volumes and resistivities of the component parts. With reasonable approximations a simple expression (Eq. 6) is obtained in which relative resistance variations, and thus variations in the magnitude of the impedance are expressed in terms of relative

volume changes. The *expression for resistivity* itself can also be a valuable tool for interpreting variations in the basic impedance

In Eq I 10

$$\rho = \left(1 + \frac{V_A}{V_E}\right)\rho_E \qquad (8)$$

V_A and V_E are volume fractions of a volume V_C, i e $V_C = V_A + V_E$ By assuming the measured value to be representative for the thorax as a whole changes in V_A can be measured by means of the air breathed However the extension of Eq 8 to hold for the thorax as a whole must be treated carefully When using the equation it is necessary to remember that within a volume element changes in V_A must be balanced by an equal and opposite change in V_E to keep the volume of the element constant Extending the relation within the volume element to hold for the entire thorax must be interpreted as requiring that the whole variation in V_A takes place without change in total V_E Thus the total volume of the thorax is increased with V_A but the volume determining the electrical field is constant

By differentiating the equation with respect to V_A the resistivity variation can be written as

$$\frac{d\rho}{dV_A} = \frac{V_C}{(V_C - V_A)^2}\rho_E \qquad (9)$$

Putting $V_A/V_C = x$ the relation can be written as

$$\frac{d\rho}{dV_A} = \frac{1/V_C}{(1-x)^2}\rho_E \qquad (10)$$

The resistance variation and hence the variation in impedance magnitude is proportional to this expression When predicting impedance variations for large volume changes from this expression it is seen that the gradient increases with the fraction V_A These theoretical results can be used to verify the nonlinear $\Delta|Z|/\Delta V$ relationships reported by Baker *et al* (10) and Hamilton *et al* (50)

The expression Eq I 14 that approximately gives the resistance between small electrodes at a distance a much larger than the electrode diameters r_1 and r_2,

$$R = \frac{\rho}{2\pi}\left(\frac{1}{r_1} + \frac{1}{r_2} - \frac{2}{a}\right) \qquad (11)$$

shows small influence of the distance a From the results on basic impedance *measurements* in Part III it is found that for some leads the impedance values divided by interelectrode distance may deviate less than the values without *correction for electrode distance* This result can be explained by the fact that the section through the electrodes is not circular but elliptic

The importance of taking the inter-electrode *distance into account must however not be* overestimated

Eq 11 can also be used to calculate an approximate value for the mean thoracic resistivity somewhat dominated however by the resistivity close to the electrodes Applying the equation to the values in Part III the mean resistivity of the thorax of a newborn infant can be estimated to be some 500 ohm cm For adults the corresponding value can be estimated to be about 1000 ohm cm by using values from for instance Pasquali (85) and Baker and Geddes (14) This latter value can be compared with values of the same magnitude measured with various other methods on animals (45) The lower resistivity of the lungs in newborns as compared with adults is in accordance with the higher tissue/air ratio that is evident in the microscopic structure of the neonatal lung

Physiological background of variation in impedance with respiration

Simultaneous recording of variations in air volume and impedance over the thorax with respiration give graphs which accord well With increasing air volume during inspiration the impedance increases (II III 17 42 44) indicating a gradual increase of the resistivity of the lungs (I II III)

On the other hand examination of a constant volume containing densely packed non-conductive equal spheres surrounded by a conductive fluid reveals that with the exception of extreme situations the resistivity does not alter with

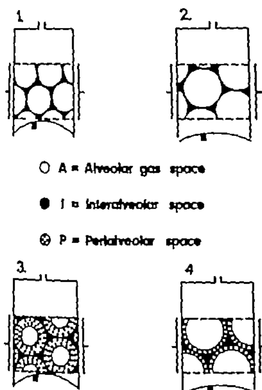


Fig 1 Physical lung model with
1 2 small amount of fluid.
3–4 larger amount of fluid

change in diameter of the spheres The absolute relation between conductive and non-conduct e material remains unchanged whether the spheres are large or small. In comparison w th a sche matic lung model according to F g 1 (1 *), the ratio alveolar space/interalveolar space is const nt within a fixed volume of lung No change in impedance then takes place with inspiration

Absolutely for the lung as whole the same reasoning implies that n increase in air volume (l eolar pace) also requires an increase n total nteralveolar space which then must be f lled with mov ble substance from outside the lveola region. Deviation from a round al eolus in piration will require further interal eolar substance during inspiration a any hange in hape during increase in size is in the direction of increasing roundness with a relatively faster increase of interalveolar space

Such an increase of interalveolar substance can in principle occur in two ways, either by addition of movable substance from a source outside the lung or by redistribution of substance within the lung in accordance with the lower part of Fig 1 (3–4) The model with densely packed non-conductive spheres is then abandoned and another volume the perialveolar space is added. Redistribution of substance from the perialveolar to the interalveolar space decreases the amount of externally supplied fluid required to fill the increasing interalveolar space during inspiration. The ratio air/fluid in the lung thus rises, resulting in an increase of the impedance

Movable substance is primarly fluid, and especially blood permitting both reduced out flow and increased inflow to the lungs during inspiration. Perialveolar interstitial fluid as well as lymph may also contribute the lymph to a limited extent in as much as there most probably exists an efficient valve system even in newborn infants (103 104 105)

The lymph vessels thus constitute one-way roads in the centripetal direction. The flow probably varies with respiration but the net flow out of the lungs during a breath is negligible as judged from the figures of 2–4 g per kg body weight and hour in newborn lambs (53 103).

Large amounts of perialveolar fluid in the lung at end-expiratory level thus reduce the increment in the total pulmonary fluid volume during inspiration, resulting in a larger im pedance deflection per unit air volume variation.

Assuming that the electrical current flux pat tern is constant which is reasonable at least in quiet respiration (I) a variation in resistance will be due to the change in the resistivity of the lungs. With certain approximations, the following relation between conductive and non-conductive volumes in the lungs can be considered as valid for respiration (I)

$$\frac{\Delta Z_l}{Z_0{}^l} = \frac{V_A}{V \pm V_E}\left(\frac{\Delta V}{V_A} - \frac{\Delta V_E}{V_E}\right) \quad (12)$$

Examination of the theory concerning the relation air/fluid as revealed by the transthoracic impedance (TTI)

To test the validity of TTI as a means of revealing not only variations in air volume but also blood volume of the lungs experiments were performed on anaesthetized cats (II) Pulmonary blood volume as measured by a radioactive technique was made to vary by stepwise withdrawal and retransfusion of blood A constant finding was an increase in impedance with decreasing blood volume and *vice versa* A very close linear relationship was found in the cats studied between the two variables relative impedance change and relative blood volume change No concomitant variation in pulmonary air volume was noted

Pulmonary blood volume was also changed by other means With sudden occlusion of the aorta and the common carotid arteries a resulting rise in pulmonary blood volume occurred simultaneously with a falling impedance Constant infusion of norepinephrine known to constrict the heart makes pulmonary blood volume rise and impedance fall This last finding is of special interest as the heart in these studies was included in the electric field measured More important for the impedance characteristics of the electric field than the contracted blood volume of the heart is obviously the increase in pulmonary blood volume

This is not surprising as in accordance with the expression Eq I:2 blood has a more dominant role concerning impedance when entering the lung than when situated in a volume of low air density The relatively minor part played by the blood inside the heart has previously been pointed out by Nyboer (78)

It was also possible to increase impedance by a sudden rise in end-expiratory pressure manifesting itself as a higher functional residual capacity without any noticeable change in pulmonary blood volume—this finding provides strong evidence against the belief that contact impedance is responsible for the impedance change, in that the higher intrathoracic pressure would if anything tend to create better conta between skin and electrodes which in th situation are externally mechanically fixed.

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Practical aspects of the application of the method to the newborn infant and treatment of the signals obtained

When selecting the positions for the electrodes the aim is to involve as much as possible of the lung parenchyma in the electric field and to avoid other structures. The best ocular control of the electrodes is afforded with the electrode pairs placed bilaterally in the mid-axillary line

and displacement of their position is comparatively small as the infant moves. The mediastinum forms a part of the electric field with this lead influencing basic impedance but not taking part in the impedance variations caused by intrapulmonary events. It must furthermore be borne in mind that with the infant in a supine position this lead is unaffected by hydrostatically induced variations in the ratio air/fluid in the various parts of the lungs.

Sagittal leads represent a mean for the lungs as a whole with respect to hydrostatic factors. With the leads over the right lung the contribution of the heart to the electric field is reduced. The disadvantage with this lead is that the electrode pair on the back cannot be checked with the child in a supine position. When the child moves there is also the risk that the electric field will change because of displacement of the skin. However we consider this lead preferable from the theoretical point of view for the analysis of changes during respiration.

A stationary electric field is not created immediately after the electrodes are applied to the skin. Some time is required to allow the keratolytic effect of the electrode paste to act on the skin. An initial drop of impedance is regularly noted, stabilizing in 2–4 minutes (III). If quantitative impedance recording is demanded the recording can thus be started five minutes after the time of application.

The infant must remain calm during the recording as otherwise alteration displacement of the electrodes with the skin may deform the electric field.

The distance between the measuring electrodes has to be considered (I, III). By means of cineradiography the change in inter-electrode distance for the leads 1–4 and 6–7 (III) was found to range between one to three per cent from inspiration to expiration during quiet breathing.

From the measured potential distribution reported in Part I it is found by differentiating and insertion of the inter-electrode distance that one to three per cent variation in distance yield an impedance variation in the magnitude of 0.1 to 0.3 per cent. In a case with a basic impedance of 50 ohm and a tidal impedance of about one ohm the distance variation thus contributes only 5 to 15 per cent to the tidal impedance.

In the beginning of the present report certain criteria were presented as requirements for the use of the TTI method on newborn infants. In practice the method requires applying the "floating" electrodes upon the child by means of double-sealing tape which is easily done without disturbing the infant. If side-to-side recording is performed the infant is not moved, while for sagittal measuring a pair of electrodes is attached to the back after turning the infant. Thick electrode paste allows a good recording to be obtained for several days especially with a lead from side to side, without renewed application of the electrodes.

Transthoracic impedance recordings have been carried out by us for five years, on more than 400 infants, with no signs of side-effects. Because of its simple application, the procedure has not inconvenienced the infants except in a few instances with a transient irritation of the skin from tape and electrode paste. The interference of the method with routine care of the infants has been negligible. The method thus fulfils the demands of safety and simplicity in application.

The effect of hydrostatic factors on the ratio air/blood of the lungs during the neonatal period

Impedance measurements on the front and back of the thorax and bilaterally at different levels above the support have permitted investigation of hydrostatic factors (III). Comparisons have been made between impedance variations in horizontal leads at different levels induced by turning the infant.

It is a consistent finding that a lead displaying dependence on hydrostatic factors also displays a lower impedance with the exception of a lead applied to the back of the infant. This last finding is interpreted to mean that for the leads on

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quently less blood is added to the volume from outside the lung in accordance with our physical model. The air volume addition is thus relatively greater than the blood addition and the increase in impedance during inspiration is more pronounced.

This phenomenon was investigated in newborn infants with early clamping (ECI) and lat clamping (LCI) of the umbilical cord (V) These groups of infants at birth have a difference in blood volume amounting to more than 30 per cent, a difference which decreases to about 10 per cent when the infant is two hours old (70 106) The reduction can mainly be related to xtravasation of plasma in LCI To which extent this extravasation affects the interstitial fluid of the lungs has not yet been clarified.

With the method used here it is not possible t determine directly whether the fluid is intravascular and represents blood, or whether it is situated in the interstitial space However on the basis of the studies it has been established that the relat ve impedance variations in LCI re significantly greater than in ECI which is a sign of a greater amount of movable intrapulmonary fluid in LCI

W have shown that the correlation between the ariation in air volume and TTI in the newborn nfant during a breath s good (III) If air olume and TTI are plotted against each other it i found that they correlate well during the spiratory phase In early expiration, on the other hand, th impedance always declines t a lower rat than that of the air olume nd can even rise to drop more rapidly to the initial lev l during the later phase of expiration (III V) Thi finding is interpreted s being caused by a difference in the time constant for air and blood hanges in the lung, especially in early piration During this phase the blood lea es the lung comparat vely f ster than air thu tending to increase the impedance

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Changes in the ratio air/flu d in the lungs during the first few hours of life

Basic transthoracic impedance $|Z_0|$, defined as the impedance at end-expiratory level, is a reflection of the static air/fluid relationship in the lungs Dynamic changes during respiration are superimposed upon this level.

The magnitude of TTI is influenced mainly by pulmonary air blood and interstitial fluid. For the study of TTI changes during the adaptation process in the immediate post natal period two groups of infants with known difference in total blood volumes have been chosen The groups consist of newborn infants with early or late clamping of the umbilical cord (IV V) Reported values show that LCI have about 30 per cent larger blood volume than ECI at 15 minutes of age. At 24 hours the difference has decreased to about 10 per cent (106)

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Dynamic correlation of variations in the ratio air/blood in the lungs of newborn infants during respiration

On the basis of the conditions previously discussed (negligible skin impedance and approximately unchanged current flux pattern) an impedance change during respiration will reflect variations in the resistivity of the lungs The regularly observed increase in TTI during inspiration means that comparatively more air than fluid is supplied to the part of the lung being examined This is a contradiction of our theoretical designation of the lungs as having a structure similar to densely packed spheres (Fig 1 (1–2)) and indicates the presence of a so-called perialveolar space (Fig 1 (3–4)) Substance displaceable between the perialveolar and interalveolar space thus exists in the lungs

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The negative pleural pressure arising during normal respiration is transferred to the interalveolar space while the capillaries, in connection with the alveolar wall are also subjected to *the higher alveolar pressure (75) and* thus tend to evacuate into larger vessels

Besides these strictly intrapulmonary displacements an increase in the total blood volume in the lung generally occurs during inspiration. A reduced pulmonary vein flow was determined already in 1943 by Dupee and Johnson (39) and was regarded as an increased capacity of the vascular bed of the lungs during inspiration This was later confirmed both in pulmonary specimens (72 88) and *in vivo* (38 112) and applies both to normal respiration and to intermittent positive pressure ventilation.

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This phenomenon was investigated in newborn infants with early clamping (ECI) and late clamping (LCI) of the umbilical cord (V). These groups of infants at birth have a difference in blood volume amounting to more than 30 per cent a difference which decreases to about 20 per cent when the infant is two hours old (79 106) The reduction can mainly be related to extravasation of plasma in LCI. To which extent this extravasation affects the interstitial fluid of the lungs has not yet been clarified.

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Changes in the ratio air/flu d in the lungs during the first few hours of life

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Changes in the ratio air/fluid in the lungs during the first few hours of life

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Changes in the ratio air/fluid in the lungs *during the first few hours of life*

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Changes in the ratio air/fluid in the lungs during the first few hours of life

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From 12 to 24 hours a tendency towards a fall in $|Z_0|$ is noted for both LCI and ECI

Actual measurements of TTI were for technical reasons not obtained for the first 15 *minutes after birth* An extrapolation back wards to time zero by means of the suggested mathematical model provides a basis for con jecture on the events of these first 15 minutes (IV) The proposed behaviour shows an initially higher impedance for ECI *falling faster than* for LCI during this time

The expected difference in $|Z_0|$ with a lower value for LCI than for ECI originating from the difference in total blood volume is apparent at least around one hour of age The variations in $|Z_0|$ with time obvious in both groups are however more pronounced than the differences between LCI and ECI *This finding is not sur* prising when considering the profound physio-logical respiratory-circulatory changes that take place in all newborn infants and of a character to influence the resistivity of the lungs and thus also $|Z_0|$

Pulmonary air volume increases rapidly beginning with the first few breaths and an essen tially stable FRC is created within the first half hour of life (65) After this time a slight increase in FRC may be noted especially in LCI *who are known to have a delay of pul* monary air filling with a small FRC during *the first six hours as compared with ECI (80)*

Pulmonary blood volume is influenced by pressure and flow in the central circulation and also as judged from our animal experiments (II) by total blood volume Pulmonary blood flow increases immediately after the onset of respiration due to a falling pulmonary blood flow resistance as the vasoconstriction in the *arterioles diminishes* An increase of the volume of the pulmonary vascular bed distal to these vessels, and hence in pulmonary blood volume is thus to be expected *After one hour the right-to-*left shunting in the central circulation has dis-appeared implying a ten fold increase of pulmonary blood flow as the entire right heart output is directed towards the lungs (48) A shift to a progressively increasing left right shunt through the ductus arteriosus further increases the pulmonary blood flow *Maximal* flow occurs probably from about three to five hours of life after which time a gradual con-striction of the ductus arteriosus makes the left right shunt disappear some time during the latter part of the first day Although no simple relation exists between flow and volume the pattern of change is in all probability similar

Concerning pulmonary interstitial fluid no direct information is available from newborn infants Animal studies have shown a pro-gressive distension of the interstitial space during the first half hour after birth (5) Analysis of the lung lymph suggests that the fluid mainly consists of bronchial fluid transferred to the interstitial space (103) The distension diminishes rapidly during the second half hour and more slowly for the following four to six hours

Variations in $|Z_0|$ in our studies represent the net result of variations in pulmonary air blood and interstitial fluid with partly counteracting *effects on the impedance*

For the interpretation of variations in $|Z_0|$ it is convenient to discuss the consecutive time periods separately For the first *15* minutes available information is confirmed to calculated theoretical values (IV) Though hypothetical the *results appear reasonable* and easily explained. A rapid decrease in $|Z_0|$ would be caused by *the fast increase of pulmonary* blood volume as well as interstitial fluid volume The initially lower total blood volume in ECI than in LCI, also reflected in a smaller pulmonary blood volume (higher $|Z_0|$) promotes a compensatory peripheral vaso-constriction with a further increase of pulmonary blood volume as a result The fall in $|Z_0|$ is then faster for ECI and at 15 minutes no definite difference between the two groups is noted in $|Z_0|$ It is well established that the newborn infant has *an efficient control of peripheral circulation* with pronounced increase of blood flow resistance in response to hypovolemia (23 24 108) Actual measurement of $|Z_0|$ during the first *15* minutes would probably give lower values than those calculated as the extrapolation does not take

the large initial increase of pulmonary air volume into consideration.

Measured values from 15 to 30 minutes show a falling $|Z_0|$. During this period pulmonary blood volume and interstitial fluid (as judged from animal studies) are both increasing with an influence on $|Z_0|$ prevailing over the effect of a still increasing air volume. The results are similar for LCI and ECI.

The stable level of $|Z_0|$ between 45 and 75 minutes proves that there is a constant air/fluid ratio in this period. As the air volume is unchanged or increases only slightly the fluid volume also has to be constant. The interstitial fluid volume has now passed its peak value and is falling as the main part of the bronchial fluid is already transferred to the interstitium. The draining effect of the pulmonary lymphatics is dominating, resulting in a progressive shrinkage of the interstitial space. Obviously an increase of pulmonary blood volume is balancing the decreasing interstitial fluid.

The different $|Z_0|$ levels for the LCI and ECI suggest that a lower total blood volume in ECI causes a lower fluid volume as well, but a smaller FRC in LCI may also contribute to the difference.

The increase in $|Z_0|$ from the second to the twelfth hour of life is the result of the combined influence from all three variables described, acting in the same direction. Pulmonary blood volume is presumably at its maximal level in the first part of this period, after which the volume tends to fall as the ductus arteriosus starts to close. The decrease in interstitial fluid volume has not yet ceased and the FRC is constant or increasing slightly. The faster rise of $|Z_0|$ in LCI is possible to explain from a more pronounced increase of FRC in these infants, starting from an initially lower level.

The change in $|Z_0|$ as studied during the second hour (Part IV) and later (Part V) shows the same course in both Parts but a difference in level is noted at two hours. Due to varying electrode positions and the use of varying instrumentation the two studies are not completely compatible concerning absolute levels of basic impedance but are well compatible concerning changes of impedance.

The falling tendency for both ECI and LCI during the latter part of the first day coincides in time with, and is best explained by an increase in total blood volume as described by Usher *et al.* (100).

Effects of placental transfusion on the dynamic intrapulmonary ratio air/fluid during the first day of life

As already mentioned LCI have a larger total blood volume than ECI. This difference is reflected in static pulmonary blood volume and lower $|Z_0|$ for LCI, though statistically significant only around one hour after birth (IV). The difference between the groups has a tendency to diminish with the difference in total blood volume.

In spite of these rather modest differences in $|Z_0|$ our studies of dynamic impedance changes with respiration have revealed deviations in the course of extrauterine adaptation of ECI and LCI (V). During the whole time of study from 2 to 24 hours of age, LCI show a larger impedance deflection per unit air volume change with respiration ($|Z_T|/V_T$). In accordance with earlier considerations this finding is a sign of more perialveolar movable intrapulmonary fluid consisting of blood and interstitial fluid. *The relative amount of blood being moved in and out of the lungs with respiration is thus smaller in LCI.*

Another difference between the two groups is represented by the discrepancy between the time constants for air and fluid dynamics in *inspiration* and expiration (V). The looped relationship for a breath caused *by this discrepancy* and symbolized by $|Z_A|$ is larger in LCI than ECI at two hours, decreasing during the time of the study. The impedance recordings thus indicate that LCI have a larger pulmonary fluid volume than ECI decreasing from 2 to 24 hours after birth. The rapid fall of the fluid volume in early *expiration* as shown by a large

$|Z_d|$ implies that the larger pulmonary fluid volume to a significant part consists of blood The reduction of $|Z_d|$ points to a decrease in the pulmonary blood content during the first day which agrees well with a rising $|Z_0|$

Changes in the ratio air/fluid in the lungs can be expected to influence the pulmonary mechanical characteristics Examination of the correlation between lung compliance and the various impedance variables shows that an increase in compliance is concomitant with

increased basic impedance $|Z_0|$ (increase in the ratio air/fluid)

decrease of relative change in impedance with respiration $|Z_T|/V_T$ (decrease in amount of perialveolar fluid) and

decrease in difference between outflow of air and blood from the lungs during early expiration $|Z_d|$ (decrease in pulmonary blood volume)

GENERAL CONCI USIONS AND SUMMARY

Studies have been carried out on transthoracic impedance measurement technique and its appli cation on the newborn infant.

Instrumentation has been developed with special regard to reliable, continuous recordings and safe application to the new born. The instru ment makes use of the four-electrode technique and uses 0 2 mA peak to-peak current at 50 kHz.

Basic measurements with this current show that the thorax can be treated as a homogeneous conductor and that spherical symmetry on the whole prevails in the current distribution in the vicinity of the electrodes. These facts form the basis for calculating the influence on the im pedance that arises from geometrical factors. The influence of these factors is kept small, as is necessary by using the four-electrode technique and by maintaining the current feeding lectrodes and measuring electrodes at constant dist nce from each other

Impedance is function solely of the characteristic impedance or resistivity of the conductor when geometrical influences on the current distribution re negligible The resistivity is expressed in terms of conduct ng and non-conducting volumes Variations in transthoracic impedance can thus be expressed in terms of variations in non-conduct ve vol mes mainly air and conducting olumes principally fluids, in the thorax

A mathematical physiological mod l for respiration has been developed n order to facilitate the understanding of impedance signals as repre sent tiv of olume variations in the lungs.

The method allows changes in the ratio air/ fluid in the lungs to be interpreted, and the inter pretation ha been tested experimentally In studies on cat separate and independent variations of pulmonary blood olume and pulmonary ir volume have confirmed that the impedance measured at end-expiratory level denoted basic transthoracic impedance $|Z_0|$ is a function of these variables, directly proportional to air volume change and inversely proportional to blood volume change

Methodological studies in newborn infants have been performed to determine the most suitable electrod positions and the requirements for stable, reproducible recordings

In the studies of newborn infants intrapulmonary hydrostatically dependent variations in the ratio air/blood have been found detectible with the impedance technique

Investigation of static basic impedance $|Z_0|$ from the age of 15 minutes to 24 hours has revealed a pattern with four different stages The resistivity of the lungs decreases up till 30 minutes of age then remains roughly stable to increase from the second hour of life to around 12 hours, followed by a tendency towards a fall during the latter part of the first day These findings are interpreted as the net result of variations in three different variables volume of air volume of blood and volume of interstitial fluid in the lungs. The initial impedance fall reflects an increasing pulmonary blood and interstitial fluid volume During the second stage impedance levels off as fluid is being drained out of the interstitial space through the lymph vessels but the total lung fluid is virtually constant as the blood volume increases further with a fairly constant air volume. The rise in impedance during the following hours is considered to be a combined effect of decreasing interstitial fluid decreasing blood volume and an augmentation of the air content of the lungs. A possible fall in basic impedance during the latter part of the first day of life is most probably a reflection of an overall increase in blood volume

By combining the impedance method with measurements of air volume change it is possible to study the dynamic variations in pulmonary fluid and blood volume with respiration The relative impedance change with a breath $|Z_T|/V_T$ is a function of pulmonary blood and perialveolar fluid as explained with the theoretical model created for volume variations with respiration Another index of pulmonary blood volume $|Z_d|$ is a measure of "excess" blood in the lungs during inspiration leaving the lungs early in expiration.

The results indicate that pulmonary blood volume increases during inspiration and that this increase is at least partly due to an increase of the so-called interalveolar space With a large amount of blood in the lungs at end-expiratory level, as is the case after late clamping of the umbilical cord, an intrapulmonary shift of fluid allows a relatively smaller amount of blood to be moved with respiration in and out of the lungs

Changes in these variables and their correlation with changes in mechanical properties of the lungs allow the conclusion that infants wit late clamping of the umbilical cord have a initially larger amount of pulmonary fluid an blood as compared with early-clamped infants. larger fluid and blood volume in the lungs i furthermore correlated with a smaller pul monary compliance

Transthoracic impedance measurement mak it possible to measure a new physiologic dimen sion the air/fluid ratio in the lungs, an together with determination of air volum change allows the fluid fractions in the lungs t be studied.

The simple and easy application to infant opens the possibility of continuous longi tudinal studies The method is from both th theoretical and practical points of view fr of complications.

It is concluded that transthoracic impedanc measurement is as used here a new safe an valuable tool for further study of physiologi and patho-physiologic respiratory-circulator adaptation in the newborn infant

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CONTENTS

PRESIDENTIAL ADDRESS

TUOMAS PELTONEN

From the Children's Hospital, University of Turku, Turku, Finland

Several hundred people working with children — doctors, psychologists, physicists and chemists — have come together from Iceland, Norway Denmark, Sweden and Finland for the XVIth Scandinavian Paediatric Congress. The congress is larger than any of its predecessors, both in the number of participants and in the number of scientific papers.

The abstracts of the papers indicate the high standard of paediatrics in Scandinavia. They also show our excellent contacts with all parts of the world. This is something in which we can take pride and pleasure. Conspicuous advances have been made in paediatrics in our countries, advances made possible by some purposeful and imaginative thinking both in research and in practical paediatrics.

Not all countries are in such a fortunate position Indeed, world standards in paediatrics vary enormously In some countries men are working with problems that were actual here at the turn of the century In other countries the future of paediatrics is being actualized today

One of these future developments will certainly be increased specialization in the various sectors of paediatrics. Nevertheless I am convinced that no field of paediatrics — the conservative no more than the opera tive — can flourish apart from the main body of paediatrics. Even sociology and psychology in work with children can develop and give of their best to the child only if we all maintain contact with one another

Because of different standards in paediatrics, problems are defined differently all over the world. For this reason the large inter national congresses contain a great deal of material which to many is of relatively little interest. Accordingly geographically limited congresses such as the now traditional Scandinavian Paediatric Congress, are coming to have more and more importance. In co-operation with the Scandinavian Paediatric Association the various societies with a narr ower specialization in paediatrics (paediatric surgery psychiatry neurology cardiology and so on) are, through their annual meetings, becoming of increasing importance for the rapid spread of information. To be noted with pleasure is the coordination which has come into being among these societies, a coordination which has begun to show itself in Scandinavian paediatric research and which saves our resources while uniting our limited forces.

PRESIDENTIAL ADDRESS

TUOMAS PELTONEN

From the Children Hospital, University of Turku, Turku, Finland

Several hundred people working with children — doctors, psychologists, physicists and chemists — have come together from Iceland, Norway Denmark, Sweden and Finland for the XVIth Scandinavian Paediatric Congress. The congress is larger than any of its predecessors, both in the number of participants and in the number of scientific papers.

The abstracts of the papers indicate the high standard of paediatrics in Scandinavia. They also show our excellent contacts with all parts of the world. This is something in which we can take pride and pleasure. Conspicuous advances have been made in paediatrics in our countries, advances made possible by some purposeful and imaginative thinking both in research and in practical paediatrics.

Not all countries are in such a fortunate position Indeed, world standards in paediatrics vary enormously In some countries men are working with problems that were actual here at the turn of the century In other countries the future of paediatrics is being actualized today

One of these future developments will certainly be increased specialization in the various sectors of paediatrics. Nevertheless I am convinced that no field of paediatrics — the conservative no more than the operative — can flourish apart from the main body of paediatrics. Even sociology and psychology in work with children can develop and give of their best to the child only if we all maintain contact with one another

Because of different standards in paediatrics, problems are defined differently all over the world. For this reason the large international congresses contain a great deal of material which to many is of relatively little interest. Accordingly geographically limited congresses such as the now traditional Scandinavian Paediatric Congress, are coming to have more and more importance. In co-operation with the Scandinavian Paediatric Association the various societies with a narrower specialization in paediatrics (paediatric surgery psychiatry neurology cardiology and so on) are, through their annual meetings, *becoming of increasing importance for the* rapid spread of information. To be noted with pleasure is the coordination which has come into being among these societies, a coordination which has begun to show itself in Scandinavian paediatric research and which saves our resources while uniting our limited forces.

PAPERS

PLENARY SESSION I

CONGENITAL HEART DISEASE IN INFANTS

CHAIRMAN BERNHARD LANDTMAN

1. CONGENITAL HEART DISEASE IN INFANTS UNDER ONE YEAR OF AGE

Introduction

B. LANDTMAN

From the Children's Hospital, University of Helsinki, Helsinki, Finland

From 1947 to 1970 5697 autopsies have been performed at the University Children's Hospital in Helsinki. The series comprised 777 cases of congenital heart disease. The incidence of these lesions has increased from approximately 5 per cent in 1947 to over 20 per cent in recent years. This shows the great part played by congenital heart disease in present-day hospital mortality statistics.

In each case congenital heart disease, data were collected from the autopsy records as well as from the clinical notes of the patients when treated in the hospital. The commonest main cardiac malformations were ventricular septal defect, transposition of the great vessels, coarctation of the aorta, hypoplastic left heart syndrome, atrial septal defect, truncus arteriosus, tetralogy of Fallot and patent ductus arteriosus.

Approximately 80 per cent of the deaths occurred during the first 6 months of life. This stresses the fact that the major problems of paediatric cardiology are confined to infants under one year of age. Only 9 of the patients treated conservatively were over 10 years old. Cardiac operations had been performed on 82 patients, half of whom were under one year of age.

The order of birth of the children with congenital heart disease did not differ from that of normal Finnish children. The birth weight was 2500 g or less in 22 per cent of the cases. Neonatal asphyxia occurred in 42 per cent of the cases. A poor weight gain was the commonest feature of the patients.

Patients with predominantly left-to-right shunts and with no shunts were frequently cyanotic. The reason for this was the high incidence of extracardiac causes of cyanosis in these cases. Cardiac failure occurred in 87 per cent and cardiomegaly was encountered in 61 per cent of the cases. Only one half of the patients revealed pathologic murmurs.

Forty five per cent of the patients had extracardiac malformations. These lesions mainly affected the alimentary and urinary organs and the skeleton. Patients with septal defects and with truncus arteriosus showed the highest incidence of extracardiac

anomalies. These lesions were equally common in boys and in girls. There was no correlation between the order of birth and the incidence of extracardiac anomalies.

Most of the patients revealed additional primary or contributing causes of death such as infections pulmonary diseases and hem orrhages. Patients with left to-right shunts showed the highest incidence of pneumonia, atelectases of the lungs and hyaline mem brane disease

The heart disease was detected during life in only 68 per cent of the cases. Diagnostic fallacies were particularly common during the first week of life

Adequate management of cardiac children requires intimate co-operation between paediatricians and special clinics. The main objective of our panel is to stress this basic presupposition. With the exception of heart operations, which require highly specialized clinics, most of the topics to be discussed are every day problems for a general paediatrician. The following main subjects will be presented in the opening addresses incidence of congenital heart disease, symptomatology and clinical diagnosis, the diagnostic value of routine X ray studies, conservative treatment, indications for cardiac surgery and heart operations.

2. INCIDENCE AND PREVALENCE OF CONGENITAL HEART DISEASE

LARS ERIK CARLGREN

From the Department of Paediatrics University of Gothenburg Gothenburg Sweden

There is no method by which the exact incidence or prevalence of congenital heart disease (CHD) can be determined at least in a population sufficiently large to permit statistical evaluation. Comparative epidemiologic studies, therefore are difficult to perform. However an investigation made on children born in Göteborg (Gothenburg) 1941—50 and 1951—60 respectively did not reveal any real change in CHD incidence from the one period to the other (1)

About four fifths of the mortality in chil dren with CHD takes place before the age of one year In Göteborg the death rate in the first year of life did not differ very much between the periods in question or a subsequent five-year period 1961—65 It is also nearly the same size in different parts of the world — about two per thousand live born infants — and is not well correlated to the general infant mortality

Among infants born with CHD a great number — perhaps about 20 per cent — have small ventricular septal defects which ultimately close, most of them during in fancy and early childhood.

The reports on prevalence of CHD in school children differ conspicuously This is probably due to dissimilarities in methods of investigation rather than to real differences. The highest figures are about four per thousand, the lowest less than one per thousand.

If the spontaneously closed VSD s are in cluded the total incidence of CHD in children born in Göteborg was nearly 8 per thousand live born. Equally high figures

Table 1 *Relative frequencies and mortality of different types of congenital heart disease in children born in Göteborg (Gothenberg), Sweden 1941—60*

Type of lesion	Total number			No. of deaths		
	Boys	Girls	All	< 1 mo.	1—12 mo.	> 12 mo.
VSD	161	140	301 [1]	22	12	8
Coarct. of aorta	48	22	70	29	8	3
Patent duct. art.	22	45	67	—	3	—
ASD (sec. & prim.)	29	27	56	8	3	4
Transposition	29	15	44	17	21	4
Aortic stenosis	24	18	42	2	3	4
Pulmonic stenosis	27	15	42	5	2	3
Anomaly of Fallot	19	16	35	6	4	8 [2]
Idiop. pulm. dilat.	9	17	26	—	—	—
Anomal. pulm. veins	14	8	22	2	4	2
Hypopl. left heart	11	6	17	13	3	—
Pers. a-v canal	8	5	13	1	10	2
Single ventricle	6	6	12	6	1	4
Tricusp. atresia	6	3	9	—	2	3 [2]
Pers. truncus art.	4	5	9	7	1	—
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All types	452	386	838	140	91	54

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2 two were > 16 years.

have only been reported by few other investigators. The relative frequencies of the *different types of CHD* and the mortality in each are shown in the Table 1

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3. ASPECTS ON THE CLINICAL DIAGNOSIS OF CONGENITAL HEART DISEASE IN INFANCY

M. MICHAELSSON

From the Department of Paediatrics University Hospital, Uppsala, Sweden

The diagnostic difficulties *especially* in early infancy are illustrated by a few figures from a study of an unselected autopsy material covering a period of seven years (1961—1967) The material comes from the northern part of Sweden with a population of about 2 million inhabitants, the number of live born infants being 25 per cent of the whole number in the country The main cause of death was reported to be congenital heart disease (CHD) in 200 cases. In 10 per cent of the material CHD *was thought* to be the cause of death but at autopsy other diseases were found

anomalies. These lesions were equally common in boys and in girls. There was no correlation between the order of birth and the incidence of extracardiac anomalies

Most of the patients revealed additional primary or contributing causes of death such as infections, pulmonary diseases and hemorrhages. Patients with left to-right shunts showed the highest incidence of pneumonia, atelectases of the lungs and hyaline membrane disease

The heart disease was detected during life in only 68 per cent of the cases. Diagnostic fallacies were particularly common during the first week of life.

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instead (for instance diaphragmatic hernia, septicemia and bronchopneumonia) — In 20 per cent of the cases, CHD found at autopsy was not disclosed or only suspected before death. In this study the importance of im proved diagnostic accuracy is illustrated by the fact that 40 per cent of the CHD s found at autopsy could have been palliated or corrected.

The younger the infants the more vague and less specific are the symptoms caused by severe congenital heart disease Other diseases in early infancy give symptoms similar to those of CHD Examples of such diseases are severe intracranial disturbance, primary pulmonary diseases, septicemia, hy pothermia diaphragmatic hernia esophageal atresia, and overtransfusion.

The most common symptoms in small infants with cardiac disorders are cy anosis, congestive heart failure abnormal heart rate and cardiac murmurs. Cyanosis, at any time after birth, even less severe if persisting in spite of oxygen therapy is an important argument in favour of CHD and should indicate that the infant should be referred, without delay to a paediatric cardiologist. Peripheral hematocrit normally varies widely but if the hematocrit is un changed or increases with time this is of important guidance Signs compatible with congestive failure including tachycardia, increased respiratory rate, gallop sounds, enlargement of liver and spleen, loud heart sounds, abnormal pulses and cyanosis should be searched for and registered at frequent intervals in suspected cases. Bradycardia may be a sign of hypoxia. A great number of the infants with severe CHD have no heart murmurs or only grade I—II.

Repeated ECG tracings (including precordial leads) and conventional X ray ex amination are important aids in the diagnosis whether the infant has a CHD or not, but especially during the first two weeks of life the ECG and the roentgenological appearance of the heart are often within normal limits. Many other disorders give abnormal ECG tracings and abnormal roent genological findings of the heart and pulmonary vessels. The lack of specificity of abnormal findings in CHD is further illustrated by the fact that hypoglycemia and metabolic acidosis or respiratory acidosis or a combination of both forms of acidosis are common in infants with CHD

Recommendation of literature for further studies

Rowe, R. D & Mehrizi, A. The neonate with congenital heart disease, In *Major Problems in Clinical Pediatrics, Vol. V* W B. Saunders, Phi, Lo To 1969

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4. ROUTINE X RAY

U RUDHE

From the Department of Paediatrics, Karolinska Sjukhuset, Stockholm, Sweden

5. MEDICAL TREATMENT OF INFANTS WITH CONGENITAL HEART DISEASE

ALF WENNEVOLD

From the Cardiovascular Laboratory of Medical Department B Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

The indication is mainly congestive heart failure, but also arrhythmias, infections, anoxia and metabolic acidosis together with acute myocarditis and fibroelastosis.

The treatment includes digitalis, diuretics, oxygen and antibiotic therapy

Digitalis. The indication is congestive heart failure and tachyarrhythmias (3). Contraindication is only digitalis intoxication. Digitalis may well be used — with caution — in the presence of ventricular tachycardia or v block.

The drug of choice is digoxin parenterally or — preferably — orally as elixir (0 05 mg/ml) The dosages recommended differ in the various textbooks but are in general too small, according to our experience in the Queen Louise Children s Hospital in Copenhagen. We recommend a total digitalizing dose of 0.1 mg/kg, given in three divided doses within 24 hours (usually one-half initially and then one-quarter in 6—8 hours, and the last quarter in another 6—8 hours) The maintenance dosage is usually one-quarter of the total digitalizing dose. We are inclined to use the same dose orally and parenterally though it is widely stated that the parenteral dose should be only 2/3—3/4 of the oral dose.

In premature infants with their immature renal function the digitalizing dose is claimed to be less — and this is also to some extent the rule for full term infants in the first month of life 0 04—0 05 mg/kg parenterally or 0 06—0.08 mg/kg orally Again we are more inclined to use our usual total digitalizing dose initially and then if necessary reduce the dose. Others (3) have concordantly stated that in premature infants small repeated doses used until digitalization is achieved usually total an amount similar to that required for full-term newborn infants.

Lower doses are needed if renal failure is present (Table 1), as the elimination is decreased, and should be used with care in conditions with loss of potassium (treatment with diuretics or steroids, presence of diarrhoea)

An electrocardiogram should always be recorded before digitalization, and during digitalization the patient should be followed closely — clinically and with electrocardiograms — as tolerance of digitalis varies considerably

The effect of adequate digitalization is seen on a significant reduction in heart rate and respiratory rate and in improvement in general condition. Later reduction in liver

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The effect of adequate digitalization is seen on a significant reduction in heart rate and respiratory rate and in improvement in general condition. Later reduction in liver

size and in peripheral oedema is seen. The patient is more relaxed stops perspiring and coughing, and feeds better

Digitalis intoxication (1) manifests itself through gastrointestinal symptoms — anorexia and vomiting — and through dysrhythmias (due to depression of the conduction system or to increased myocardial irritability) Extrasystoles may be seen (multifocal much less common bigeminy) but more often a v block (prolonged PQ interval or high degree a v block) sino-auricular block and significant sinusarrhythmias are *encountered* *All kinds of* dysrhythmias may be seen, however and if there is any doubt, *digitalis* intoxication should be strongly suspected.

The treatment of digitalis intoxication is first and foremost to stop the drug With normal renal function the toxicity usually lasts 1—3 days, but may last for about one week. Potassium may be given (unless there is hyperpotassaemia impaired renal function or high degree a v block) Diuretic treatment may be temporarily discontinued to avoid further potassium loss. Acid-base status and electrolyte imbalances (e.g hypomagnesemia) should be corrected. Diphenylhydantoin, beta receptor blocking agents, procaine amide and lidocain may be used in tachyarrhythmias, while atropine, isoprenaline — or even a pacemaker! — may be tried in high degree a v block (Table 2) Ventricular fibrillation is treated by DC countershock.

Diuretics are indicated if digitalis treatment alone is insufficient (3)

Mercurials are still widely recommended but we use solely furosemid (Lasix) (2) The dose is 1—3 mg/kg orally or 0.25—2 mg/kg *parenterally* The effect is shortlasting allowing for evaluation of the effect within a short time with possible increase in dosage.

The most important side-effect is electrolyte imbalance with loss of potassium which may provoke digitalis intoxication. Potassium chloride should be given when Lasix is used for more than a few days, even when a normal serum potassium is present the serum level does not reflect the potassium depletion of the myocardium.

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Table 1 *Dependance of maintenance dose of digoxin on kidney function*

	Creatinine clearance (ml/min.)	Maintenance dose as percent of loading dose
Normal	100	34.3 (= 1/3)
	50	[illegible]3.2 (= 1/4)
	25	[illegible]0 7 (= 1/5)
Anuria	0	14.4 (= 1/7)

(After Jelliffe R. W An improved method of digoxin therapy *Ann Int Med*, 69 703 1968).

Table 2. *Dosage of drugs used in treatment of digitalis intoxication*

Potassium chloride	0.3 mEq/kg per hour i.v up to [illegible]0—3 0 mEq/kg per 4 hours
Magnesium sulfate	0.[illegible]5 g/kg/dose orally 0 1—0.2 ml 50 %/kg/dose i.m. (may be repeated q 4—6 hours) 1 5 mg/kg/dose (= 5 8 ml 3 %/kg/dose) i.v over 1 hour
Diphenylhydantoin	3—8 mg/kg/24 hours
Propranolol	0 1 mg/kg i.v (3—4 times daily) 1 mg/kg orally q 6 hours
Procaine amide	10—30 mg/kg i v over 5 minutes
Lidocaine	1 mg/kg i.v (diluted in 5 dextrose in water)
Atropine	0 01 mg/kg/dose
Isoprenaline	4 mg/1000 ml 5 / dextrose in constant drip until effect (total dose about 0,001—0 003 mg/kg per 10 minutes)

All i.v administrations should be controlled and adjusted by continous ecg.-monitoring.

Sodium restriction is usually unnecessary Treatment with *oxygen*, correction of *electrolyte imbalance* and of *acidosis* need little elaboration. The correction with bicarbonate of metabolic acidoses in cyanotic infants is emphasized.

Posture in a sitting or semi-sitting position is sometimes appropriate and possible in a modern infant chair

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6 INDICATIONS FOR SURGICAL TREATMENT OF CONGENITAL HEART DISEASE IN INFANCY THE BALLOON ATRIAL SEPTOSTOMY

B. SØRLAND

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The treatment of digitalis intoxication is first and foremost to stop the drug. With normal renal function the toxicity usually lasts 1—3 days, but may last for about one week Potassium may be given (unless there is hyperpotassaemia, impaired renal function or high degree a v block) Diuretic treatment may be temporarily discontinued to avoid further potassium loss. Acid base status and electrolyte imbalances (e g hypomagnesemia) should be corrected. Diphenylhydantoin beta receptor blocking agents, procaine amide and lidocain may be used in tachyarrhythmias, while atropine, isoprenaline — or even a pacemaker! — may be tried in high degree a v block (Table 2) Ventricular fibrillation is treated by DC countershock.

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Mercurials are still widely recommended but we use solely furosemid (Lasix) (2) The dose is 1—3 mg/kg orally or 0.25—2 mg/kg parenterally The effect is shortlasting, allowing for evaluation of the effect within a short time with possible increase in dosage.

The most important side-effect is electrolyte imbalance with loss of potassium, which may provoke digitalis intoxication. Potassium chloride should be given when Lasix is used for more than a few days, even when a normal serum potassium is present the serum level does not reflect the potassium depletion of the myocardium.

Another side-effect of the intravenous use of a large dose is too fast a decrease of the blood volume with shock and collapse.

Table 1 *Dependance of maintenance dose of digoxin on kidney function*

	Creatinine clearance (ml/min.)	Maintenance dose as percent of loading dose
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Diphenylhydantoin	3—8 mg/kg/24 hours
Propranolol	0 1 mg/kg i.v (3—4 time daily) 1 mg/kg orally q 6 hour
Procaine amide	10—30 mg/kg i.v over 5 minutes
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prevent obstructive pulmonary vascular disease, it is indicated with early

a) ligation of a moderate or large patent ductus,

b) banding of pulmonary artery in ventricular septal defect.

A survey of 3 years' experience with the balloon atrial septostomy

Twenty patients with transposition of the great arteries and 2 with total anomalous pulmonary venous return were treated, half of them in the first 2 weeks of life. One patient died of perforation of the left atrial wall, with hemopericardium and bradycardia. Another 4 have died since (two of them coming too late to septostomy one after explorative thoracotomy one after intracranial venous thrombosis) Four needed a repeated balloon septostomy 3 weeks to 3 months after the first. The procedure had only transient effect in two, and could not be accomplished in one. These three had a surgical atrial septal defect. Rupture of the balloon occurred in 40 / of the procedures, and was experienced also in the newborn. Of the 17 survivors, 5 have an observation period of 1—2 years, and 3 more than 2 years, awaiting a Mustard's procedure.

7 CARDIAC OPERATIONS

A. SENNING

From the Ka tonsspital, Zürich, Switzerland

2. Severe valvular aortic stenosis, with left heart failure (after medical treatment, if possible)

3 Coarctation of the aorta, with congestive heart failure without definite improvement after medical treatment for 24—36 hours (and in particular with associated cardiac anomalies which need additional surgical treatment)

B Left to-right shunt lesions Surgical treatment (ligation of a patent ductus/banding of pulmonary artery in ventricular septal defect or atrio-ventricularis communis) is indicated

1 Absolutely when heart failure or pulmonary complications are not controlled by medical therapy

2. Relatively in

a) Patent ductus with moderate or slight symptoms, or after bacterial endocarditis.

b) Atrioventricularis communis or ventricular septal defect with moderate, permanent symptoms and/or pulmonary arterial hypertension of 70—80 % or more of systemic pressures, particularly with increasing pulmonary vascular resistance on repeated heart catheterization.

C *Cyanotic lesions with VSD and pulmonic or tricuspid obstruction.*

1 In Fallot's anomaly (and functionally similar lesions) indications for shunt operations are

a) hypoxic spells, not preventable by medical means,

b) marked, permanent cyanosis, and increasing hematocrit,

c) retarded growth, irritability and failure to thrive

2. In tricuspid atresia the indications are identical. When the interatrial communication is inadequate, a balloon atrial septostomy is indicated.

D *Total anomalous pulmonary venous return.*

The majority die in infancy usually in the first 6 months

1 Balloon atrial septostomy is indicated if there is a pressure gradient between the atria.

2 Total correction is indicated when severe heart failure persists or recurs on medical treatment. Pulmonary hypertension is probably also an indication for operation even when symptoms are moderate, as pulmonary vascular resistance is likely to increase, which also increases the surgical risk.

E. *Transposition of the great arteries*

Adequate mixing between the two circulations is essential

1 Balloon atrial septostomy is indicated where no atrial septal defect is securing free inter atrial communication.

a) Absolute indication where the only mixing is through a normal ductus and foramen ovale (even when the infant is not very ill — as it may very soon be so)

b) Relative indication in ventricular septal defect or patent ductus with adequate mixing in order to decrease the load on the left atrium and pulmonary venous system, and secure adequate mixing during the following course.

2. Surgical atrial septectomy is indicated

a) when the balloon procedure is not successful, and

b) if cyanosis and heart failure later increase after a primarily successful balloon procedure.

3 In hyperkinetic pulmonary hypertension, in order to improve heart failure and

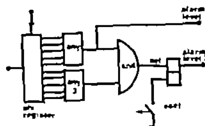


Fig. 2. The alarm circuit.

latest five positions and the second level when the conditions of the first level are realized and when any three of the first five positions are detected as non-breathing. Within this circuit one breath is allowed to occur during each five-epoch-interval and yet alarm is caused.

With this system one avoids the disadvantages of a simple delaycircuit usually used in detecting apnoeic episodes.

REFERENCES

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9 DIGITAL COMPUTER ANALYSIS OF RESPIRATORY PATTERNS IN THE NEONATAL PERIOD

U SELSTAM, P KARLBERG and T OLSSON

From the Department of Paediatrics, University of Gothenburg and Research Laboratory of Medical Electronics, Chalmers University of Technology, Gothenburg Sweden

In the neonatal period, especially when dealing with prematures or infants with disturbed functional adaptation, the pattern of respiration gives important information about the condition of the infant. A manual recording of the frequency of respiration will only give information about the mean frequency during a short epoch repeated one or more times an hour and the registration is done during subjectively chosen epochs.

The aim of this paper is to present a method of objective registration and analyzing of the respiratory pattern in the neonatal period.

The equipment consists of a tetrapolar impedance plethysmograph with an alarm unit, earlier presented in our papers (1,2), a Mingograph 81 (Elema-Schönander) and a computer (PDP 12)

The respiration is detected as described in (1,2). The time interval between two adjacent impulses is recorded in the memory of the computer programmed for a time-interval-histogram analysis. Parameters are clinically estimated. the number of epochs during the registration and the length of each epoch, the number of bins in the histogram (usually 100) and the width of each bin (usually 20 ms).

Three types of histograms are recorded

1. Zero order histogram, which during the registration continuously shows the duration of each time interval.

SESSION A I

NEONATOLOGY

CHAIRMEN POVL BRAESTRUP and *KRISTBJÖRN TRYGGVASON*

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8 MONITORING WITH IMPEDANCE PLETHYSMOGRAPHY *IN THE NEONATAL PERIOD*

U SELSTAM, P KARLBERG and T OLSSON

From the Department of Paediatrics University of Gothenburg and Research Laboratory of Medical Electronics, Chalmers University of Technology Gothenburg Sweden

In monitoring newborn infants with dis turbed functional adaptation, registration of respiration plays a dominant role. The typi cal pattern of respiration in a premature infant consists of irregular or periodic breath ing with apneic episodes of varying duration.

METHODS

One might define impedance plethysmography as a method of measuring variations in respira tion by means of changes in resistance across the chest using an alternating-current source

A four-electrode system is used to detect both the impedance signal and the ECG signal.

When detecting respiration and especially apneic *episodes one meets at least three problems*

1 The level of resistance might suddenly change. This is compensated for by an AC *connection.*

2. Variations of impedance related to changes in blood volume in the lungs must not simulate breath during apnea. This is compensated for partly by the electrode placement but mainly by a hysteresis switch, adjusted in accordance with clinical experience.

3 The monitor shall detect the apneic episodes and activate an alarm circuit after a certain period of non breathing, earlier estimated in duration based on clinical experience. A false positive or negative alarm should be avoided. We have solved this problem in the following way (Fig. 1) Time is divided into clinically estimated epochs between 0.5 and 3 s. After each epoch the monitor gives information to a shift register with *10 positions* whether breath has occurred during the epoch. In this way there is always information about breathing during the last ten epochs.

There are two levels of alarm (Fig. 2) Alarm at the first level is re-established automatically if conditions of alarm cease but manual re-establishment is needed at the second level.

In the logic circuit used to detect apneic episodes the first level of alarm is reached when non-breathing is detected in any *four* of the

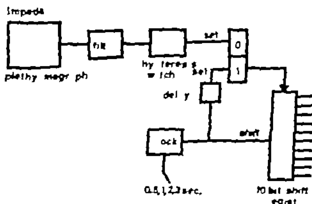


Fig 1 The monitor

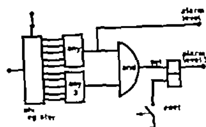


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Three types of histograms are recorded.

I Zero order histogram, which during the registration continuously shows the duration of each time interval.

2 Histogram of order —1 which gives information about the mean frequency of respiration during each epoch.

3 Histogram of order +1 in which the X axis is divided into the clinically estimated number of bins and on the Y axis are plotted the number of impulses in the different bins. In the last bin (usually no 100) is recorded the total number of apneic episodes (usually time intervals exceeding 3 s in which no detection of breath has occurred) There are possibilities of varying the scale on the Y axis and of adding the content of adjacent bins on the X axis.

The following calculations are made from the histograms

1 The total number of detections during each epoch and during the whole registration.

2 The mean frequency

3 The total number of apneic episodes and its relation to the total number of detections

4 The standard deviation of the histogram.

5 The relative height of the peaks of the histogram, i.e. the most frequent frequency of respiration, and their relation to the total number of detections.

Repeated studies are performed with

1 Healthy newborn infants

2 Prematures of different gestational age

3 Newborn infants with disturbed functional adaptation.

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10 MATURITY ESTIMATION IN NEWBORN INFANTS MOTOR AND SENSORY NERVE CONDUCTION VELOCITIES

S BLOM and O FINNSTRÖM

From the Laboratory of Clinical Neurophysiology and Department of Paediatrics University Hospital, Umeå Sweden

There are two main reasons for estimating maturity (or development) in newborn infants.

1 Gestational age is unknown in some cases. Sometimes it is important to know the approximate age in order to understand symptoms and to institute correct treatment in the newborn period.

2. By comparing groups of newborn infants, i.e. small for-date infants and full term infants with birth weight appropriate for the gestational age, it is possible to evaluate the influence of pathological conditions, i.e intrauterine growth retardation, on maturity

I.

In earlier work we showed that there is a positive correlation between gestational (or postmenstrual) age and motor nerve conduction velocities in the ulnar and peroneal nerves. Normal values for motor conduction velocities in the newborn period were presented (1)

180 newborn infants have previously been studied and different methods for estimating maturity were compared. Of this series, 60

Table 1 *Results*

	Small for-date infants N = 20	Full term, normal birth weight N = 20	Pre-term, normal birth weight N = 20
Mean moto conduction velocity ulnar nerve, m/sec	26 5	27.5	22 3
Mean birth weight, grams	2142	3478	2143
Mean post-menstrual age t examination, days	261	281	250

infants were selected for the present study according to the following criteria

1 20 full-term, small-for-date infants (birth weight below — 2 S. D according to Swedish standards, (2)) in whom no major anomalies or pathological neurological signs were present in the newborn period.

2. For each small for-date infant, one full term infant with normal birth weight and of equal gestational age was selected, 20 infants in all. Their mean gestational age was the same as that of the *small for-date infants.*

3 For each small-for-date infant, one pre-term infant with the same birth weight, ppropriate for the gestational age, was selected, 20 infants in all. Their *mean birth* weight was the same as that of the small-for-date infants.

Pre-term infants have significantly lower mean motor conduction velocity than do full term infants, as has been *previously shown* (1) This is probably due to a difference in myelination at birth. Full term, small for date infants have a mean conduction velocity that is not significantly lower than that of the full-term infants with normal birth weight. This probably means that in the majority of small for-date infants, *peripheral* myelination is largely unaffected by the intrauterine undernutrition causing growth retardation.

This is at variance with the results *of* clinical evaluation of neurological maturity in which small-*for*-date infants had signifi cantly lower neurological scores *than did* *full-term infants* with normal birth weight (3).

II.

In another material consisting of 20 new born infants of various gestational ages and birth weights, motor and sensory nerve conduction velocities were measured in the ulnar and median nerves. The sensory conduction velocity could be measured by using a computer for average transients. The action potentials of the nerves were recorded over the wrist using surface electrodes. The stimulation was done over the fingers.

RESULTS

Motor conduction velocity was slightly higher in the ulnar nerve than in the median nerve. *Motor* conduction velocities were higher in the motor fibers than in the *sensory* fibers of the corresponding nerve. There is a positive correlation between sensory conduction velocities in the ulnar and median nerves and gestational age.

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2. Histogram of order —1 which gives *information about the mean frequency of* respiration during each epoch.

3 Histogram of order +1 in which the X axis is divided into the clinically estimated number of bins and on the Y-axis are plotted the number of impulses in the differ ent bins. In the last bin (usually no 100) is recorded the total number of apneic epi sodes (usually time intervals exceeding 3 s in which no detection of breath has occurred) There are possibilities of varying the scale on the Y axis and of adding the content of adjacent bins on the X axis

The following calculations are made from the histograms

1 The total number of detections during each epoch and during the whole registration.

2 The mean frequency

3 The total number of apneic episodes and its relation to the total number of detections.

4 The standard deviation of the histogram.

5 The relative height of the peaks of the histogram i.e. the most frequent frequency of respiration, and their relation to the total number of detections

Repeated studies are performed with

1 Healthy newborn infants

2 Prematures of different gestational age

3 *Newborn infants with disturbed func* tional adaptation.

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10 MATURITY ESTIMATION IN NEWBORN INFANTS MOTOR AND SENSORY NERVE CONDUCTION VELOCITIES

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There are two main reasons for estimating maturity (or development) in newborn infants

1 Gestational age is unknown in some cases. Sometimes it is important to know the approximate age in order to understand symptoms and to institute correct treatment in the newborn period.

2 By comparing groups of newborn infants i.e small for-date infants and full term infants with birth weight appropriate for the gestational age, it is possible to *evaluate* the *influence* of pathological conditions, i.e. intrauterine growth retarda tion, on maturity

I.

In earlier work we showed that there is a positive correlation between gestational (or postmenstrual) age and motor nerve conduction velocities in the ulnar and peroneal nerves. Normal values for motor conduction velocities in the newborn period were presented (1)

180 newborn infants have previously been studied and *different methods for estimating* maturity were compared. Of this series, 60

ABO-immunisation cases and only two of the hyperbilirubinemia cases had the same phenomenon. Besides the furcation, another type of abnormal phonation, namely bi phonation, was observed in 22 of the present cases.

Most of the variables in the groups of Rh- and ABO-immunisation have greater devia tions from normality than in the group of hyperbilirubinemia without blood group incompatibility at the same bilirubin levels. This also supports the generally accepted fact that infants suffering from a haemolytic disease are in greater danger of developing kernicterus than those with hyperbiliru binemia without incompatibility in blood groups.

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12. PRE- AND PERINATAL ETIOLOGICAL FACTORS IN CHILDREN WITH EPILEPSY AND OTHER CONVULSIVE DISORDERS A PROSPECTIVE STUDY

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From the Department of Paediatrics, University Hospital, Copenhagen, Denmark

The Paediatric Department (professor P Plum) of the University Hospital, Copenhagen, is conducting a follow up investigation of 8425 children born in the hospital in 1959—1961 During the first year of life, 19 infants died after the neonatal period, (first 28 days) 98 / of the surviving were re-examined one year old 89 / three and/or six years old.

233 cases of convulsive disorders were found 122 cases of febrile convulsions (A), 39 cases of breath-holding spells (B), 21 cases of epilepsy eight of a genuine character (C_1), 13 of a symptomatic character (C_2), 9 cases of convulsions related to acute cerebral or meningeal inflammations or injuries (D) and 42 cases (E) where the descriptions were not adequate to permit diagnosis in the groups A—D

The 233 cases found make it possible to suggest an estimated incidence of convulsive disorders in the first six years of life, excluding the neonatal period, of 4 /ₐ

This investigation was undertaken to demonstrate incidences of abnormalities in familial histories, in pregnancy delivery and the first year of life for the children with convulsive disorders and to compare these figures with a standard group from the total investigation. This group (K) consists of 1549 children with birth weights 3001—3500 g. which were found normal at one year i.e. without cerebral attacks after one month, who could stand at one year and who were without other abnormalities at the clinical examination at one year

11 CRY STUDIES IN NEONATAL HYPERBILIRUBINEMIA

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T PARTANEN and J LIND

From the Department of Paediatrics University of Oulu, Oulu, Finland, Children s Hospital, Karolinska Institutet and the Wenner-Gren Medical Research Laboratory Nortull s Hospital, Stockholm, Sweden

We have analyzed the pain cry of 45 newborns with hyperbilirubinemia This material consisted of 15 cases with Rh immunisation, 15 cases with ABO-immunisation and 15 cases with hyperbilirubinemia, where no blood group incompatibility could be demonstrated Our normal material, used as controls is reported in detail elsewhere (1) The pain cry recordings were performed during the first 15 days of life A standardized method of recording and analyzing the pain cry was used (1) For evaluating the normality or abnormality of the individual cases, a new screening method *cry score* is used (2)

Signs of developing encephalopathy were found in 21 cases during the first week of life and one case had evident manifestations of kernicterus.

As can be seen in Table 1 the pain cry in a hyperbilirubinemic infant differs clearly from that in normal material. The most obvious difference is in the maximum pitch, while minimum pitch is also higher than normal The average length and latency of the hyperbilirubinemic cry are significantly shorter than those of the normal cry Additionally a specific acoustic phenomenon, *furcation, is to be found. It is* a peculiar break in the phonation the rather high fundamental is split into a series of harmonics, making the determination of the pitch of the fundamental difficult or else forming what seems two fundamentals. This abnormal vocal cord activity can be found in the beginning or at the end of the cry Ten out of fifteen Rh immunisation cases had furcation, whereas six out of fifteen of the

Table 1 *Means medians and frequencies of different attributes in the groups of hyperbilirubinemia and normal pain cry*

		Hyperbilirubinemia sample				Normal saple N=1?0	p
		Rh imm N=15	ABO-imm. N=15	*Hyperb* N=15	*Total* N=45		
Latency sec.	Mean	1 6	1 4	1.5	1 5	2.1	0 001
	S D	0.6	0 7	0 8	0 7	1 1	
Duration, sec.	Mean	1 0	1 4	0	1 5	..7	0.001
	S.D	0.3	0.7	1 4	1 0	1 0	
Min. pitch cps.	Mean	1080	1060	750	960	420	0.001
	S.D	510	710	00	650	80	0 001
Max.pitch	Mean	030	2660	1650	2120	590	0 001
	S.D	910	1350	1120	1200	110	
Furcation	Rel freq	0.67	0 47	0 13	0 4..	0.00	0 001
Bi-phonation	Rel.freq	0.53	0 60	0 33	0 49	0 00	0 001

Two-tailed significance level for differences between normal series and hyperbilirubinemia series, based on Student s test, Wilcoxon and x^2 *tests. NS p* 0.05

bleeding and a high tendency to toxaemia and complicated deliveries was observed. There was no tendency to prematurity a slight tendency to asphyxia but a marked tendency to neonatal jaundice. There is a marked tendency to neonatal neurological symptoms, especially to convulsions. The children are socially deprived, also. Their motor development is markedly retarded.

Convulsions related to acute cerebral episodes D

The eight children in this group suggested a tendency to maternal bleeding in the first trimester and to neonatal tremor Two of the children (25 /) were reared in a children s home for more than four months during the first year There was a marked tendency to motor retardation.

Undefined convulsions E

The group of undefined convulsions is complicated by many abnormalities. The children have a familial predisposition to neuropsychiatric disorders but not to maternal epilepsy The sex ratio is elevated. A tendency to maternal bleeding is suggested and a marked tendency to preeclampsia, some tendency to complicated delivery asphyxia, neonatal convulsions and neonatal jaundice is observed. There was definite social deprivation. The motor development is characterized by extremes many children were negatively displaced by not being able to stand with support at one year but the rate of positive ability to walk alone was a little higher than in the standard group.

13 THE EFFECT OF CLIMATOLOGICAL FACTORS ON PREMATURITY AND PERINATAL MORTALITY

PAULA RANTAKALLIO

From the Department f Paediatrics, University of Oulu, Oulu, Finland

14 DISSEMINATED INTRAVASCULAR COAGULATION (DIC) IN THE NEWBORN

H. ARNESEN C. EIKA, P KIERULF E. MONN and H. VOGT

From the Dept. of Paediatrics and the Haematological Research Laboratory Dept. IX, Ullevål Sykehus Oslo, Norway

Intravascular coagulation leads to consumption of several clotting factors, among others fibrinogen, prothrombin, pro-accelerin and antihemophilic factor A. In addition platelets are consumed (3).

The laboratory diagnosis of DIC is based upon these changes. The diagnosis of DIC may be approached by different routes, by global tests, such as the TT test, or by specific tests, such as clotting factor analyses.

In the adult, if DIC is massive, the clinical picture and the laboratory diagnosis may be easily established (3) In the newborn, however the diagnosis may be puzzling even

Table 1

(figures in percentage)	A	B	C_1	C_2	D	E	K
Familial CNS-predisp	15 4	31 4	50.0	38.6	0	14.2	3 9
Maternal CNS-predisp	6.5	10.3	25 0	7 7	0	14.2	4 0
Maternal anti-epileptic treatment	0.8	2.6	25 0	7 7	0	0	0.9
Boys	56.9	41.0	50.0	69.3	50.0	59 4	47.9
Bleeding, 1st month	4.3	2.6	12.5	7 7	25 0	7 1	2 9
2nd month	7.3	6.2	0	7 7	12.5	2.4	4 7
3rd month	6 7	5.2	12.5	0	12.5	2.4	4 7
8th month	1.3	5.2	0	7 7	0	7 1	3.5
Hypertension	19.5	12.8	0	30 7	25.0	19.0	20.4
Pre-eclampsia	0 8	7 7	0	7 7	0	9.5	3.2
Medically induced delivery	14 7	12.8	0	25.3	12.5	19 0	15.1
Complicated delivery	58.5	61.5	37.5	61.5	50.0	66.7	60 4
Birth weight ≤ 2500 g	13.8	25 0	12.5	7 7	12 5	21.5	(14.1)
Asphyxia	4.9	23.1	12.5	7 7	0	12.5	6 0
Convulsions	0.8	2.6	0	7 7	0	2.4	0.2
No CNS-symptoms	87.9	82.0	75 0	76.9	62.5	90.5	86.4
Bilirubin > 17 mg%	4.9	2.6	0	23 1	12.5	7 1	4.2
Social group IV—V	46 4	51.3	62.5	61.6	0	50 0	34 8
Good housing with parents	58.4	53.2	50.0	46.2	62.5	59.5	66.2
Children's home > 4 months	4.3	8.1	0	7 7	25.0	9.5	3 3
Sitting alone before *9 months*	68.7	82.0	25.0	100 0	75 0	78.6	80.9
Standing with support at one year	96.7	48.8	62.5	46.1	62.5	66.7	100 0
Walking alone at one year	35 8	36 4	37.5	23 1	25 0	38.1	35.3
No abnormalities at one year	59.5	64 0	50 0	30 7	50 0	69 0	100.0

Conclusion

Febrile convulsions A

In this analysis it appears that children with febrile convulsions have a familial predisposition to neuropsychiatric diseases, *and that boys are more often affected than* girls. The mothers showed a slight tendency to bleeding in the first trimester The deliveries seem to be as normal as the standard group and the incidence of prematurity asphyxia, neonatal CNS-symptoms and neonatal jaundice is similar to the standard. There is a tendency to social deprivation. The *motor development was almost normal.*

Breath holding spells B

Children with breath holding spells show a high familial predisposition to neuropsychiatric disorders and an elevated tendency to maternal epilepsy *Girls* are more often affected than boys The incidence of bleeding toxaemia and birth-complications is *similar to the standard group* There is a striking tendency to prematurity neonatal asphyxia and neonatal convulsions and other abnormal neurological symptoms. These children have a marked tendency to social deprivation and to motor retardation.

Genuine epilepsy C_1

The children with genuine epilepsy have *the highest familial and maternal predisposi*tion to neuropsychiatric disorders and epilepsy There is no sex difference The group is very small so conclusions are doubtful, since *only one* abnormality in a *group of* eight gives a high rate. A tendency to maternal bleeding in the first trimester is suggested but not to toxaemia, complicated deliveries, prematurity or jaundice. One of the eight children was asphyctic and two (25 %) were hypotonic. Five of the children (62,5 %) or twice the standard were placed *in social group IV* or V There was slight motor retardation

Symptomatic epilepsy C_2

The children with symptomatic epilepsy had a *familial* and maternal predisposition to CNS diseases and epilepsy and a very high sex ratio A slight tendency to maternal

bleeding and a high tendency to toxaemia and complicated deliveries was observed. There was no tendency to prematurity a slight tendency to asphyxia but a marked tendency to neonatal jaundice. There is a marked tendency to neonatal neurological symptoms, especially to convulsions. The children are socially deprived, also. Their motor development is markedly retarded.

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The group of undefined convulsions is complicated by many abnormalities. The children have a familial predisposition to neuropsychiatric disorders but not to maternal epilepsy The sex ratio is elevated. A tendency to maternal bleeding is suggested and a marked tendency to preeclampsia, some tendency to complicated delivery asphyxia, neonatal convulsions and neonatal jaundice is observed. There was definite social deprivation. The motor development is characterized by extremes. many children were negatively displaced by not being able to stand with support at one year but the rate of positive ability to walk alone was a little higher than in the standard group.

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3rd month	6 7	5.2	12.5	0	[illegible]	[illegible]	4.7
9th month	1.2	5.2	0	7 7	0	7.1	3.5
Hypertension	19.5	[illegible]	0	30.7	[illegible]	19.0	[illegible]
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Symptomatic epilepsy C_2

The children with symptomatic epilepsy had a familial and maternal predisposition to CNS diseases and epilepsy and a very high sex ratio. A slight tendency to maternal

14 exchange transfusions were done, whereupon the urine production started, the urea and creatinin values normalized nearly and the general condition of the child improved. During the following 7 months the child has developed normally except for a slight hypertension and slightly reduced kidney function.

Finally we will comment on *Patient 3* who was beyond the neonatal period of life, but who clinically and haematologically showed a typical and fulminant DIC. She was 10 months old and healthy till she became febrile and within 12 hours died after having developed haemorrhagic exanthema, cyanosis and seizures. Neisseria meningitidis could be demonstrated in blood and spinal fluid cultures. The coagulation studies are shown in Table 1 Post mortem examination revealed haemorrhagic infarcts of both adrenals and fibrin deposits in most organs.

The results of the present study suggest that the platelet count, the one-stage-prothrombine-time (Quick) the fibrinogen concentration along with the ethanol test might be of value in rapidly establishing a diagnosis of DIC in the infant.

Combining these simple tests with a clinical alertness as to bleeding-tendency cerebral dysfunction, respiratory failure or renal insufficiency should help the paediatrician in establishing an early diagnosis of DIC in the infant.

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15 THE FIBRINOLYTIC SYSTEM IN INFANTS OF LOW BIRTH WEIGHT AND/OR SHORT GESTATIONAL PERIOD

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The aim of this investigation was: 1) to study fibrinolytic activity and the development of the different factors of the fibrinolytic system from early prematurity up to term 2) to study the changes, if any of these factors in infants with postnatal asphyxia, idiopathic respiratory distress syndrome (IRDS) and intracranial haemorrhages.

The material consisted of 197 infants in the 25th to 43rd gestational week. With respect to birth weight, length, sex and gestational period all infants were grouped according to the system proposed by Battaglia and Lubchenco, using a growth chart for normal Swedish newborns. In approximately half of the material the infants had an Apgar score of ≥ 8 at 10 min. and served as a control material to the rest of the infants with postnatal asphyxia and IRDS.

Blood was obtained from a catheter in the umbilical artery or vein. Serial sampling was performed in one part of the material. Determinations were made of. fibrinolytic activity on fibrin plates, fibrinolytic split pro-

Table I *The table shows the results of the coagulation studies in healthy full term infants, and in the three patients mentioned in the text.*

TEST	n	Mean	Range	Patient 1	Patient 2	Patient 3
Platelet count (1000 mm³)	18	234	170—437	27.5	35	32.5
Normotest (%)	18	38	25— 59			
Trombotest (%)	18	26	7— 50			
Partial thromboplastin time (sec)	14 4	123 > 3 min	81—186			
One Stage Prothrombin time (Quick) (sec)	18	18.9	14— 26	25.5	24	43
Fibrinogen (mg%)	8	253	164—337	65		97
Thrombin-time (% of control)	9 9	178 > 3 min	121—241			
Ethanol test (Godal & Abildgaard)	18	14 neg 4 pos		+	+ ?	+

when severe DIC prevails. The reason is multifarious, including a natural lability of the newborn, and a relative deficiency of several clotting factors in this period of life.

Being perplexed by a newborn with low TT and platelet values, and spontaneous subcutaneous bleedings, we have during *this last year* more carefully searched for DIC in the newborn infant. Relevant to this is the rather small number of studies on this topic (2)

The present study was undertaken, trying to determine which coagulation parameters could be of value in the early diagnosis of DIC in the newborn.

Eighteen healthy full term infants, aged *1—7 days, delivered vaginally* were studied by conventional haematological techniques.

The ethanol test was performed according to Godal & Abildgaard (1) Neither mother nor child had received vitamin K. The results are shown in Table 1 Corresponding data of three patients at the time when DIC was suspected, are also given (Table 1)

Patient 1 was asphyctic for 20 minutes at birth, the amniotic fluid was greenish. When two days old he started to vomit, became cyanotic, irritable and was treated with antibiotics. The next day haematuria developed. (For coagulation studies see Table 1) Heparin 1000 IE/day was given i.v for 4 days. The platelet number increased, as did the fibrinogen, and the ethanol test became negative.

A systolic heart murmur was heard on the 2nd day Heart failure developed and was treated conventionally from the 4th—6th day when the condition improved and the heart murmur vanished. Angiocardiography at the 8th day showed inadequate and slow filling of the right a. pulm presumably due to platelet/fibrin trapping in the vascular tree.

On the 3rd day an enlarged right kidney was palpated. *I.v urography revealed a non-*function kidney for 4 days. A biopsy taken at the 10th day showed multiple haemorrhagic infarcts with fibrin deposits. During the following 8 months the patient has developed *normally except for a hypertension which* is being further studied at present.

Patient 2 had a grunting respiration at birth, she was cyanotic and needed oxygen. The placenta and the amniotic fluid were meconium *stained This condition improved* but at 20 hours of age the cyanosis increased, seizures developed, and the spontaneous movement of extremities disappeared. Blood sugar was 0 mg% and 40 % glucose was *given i.v along with anticonvulsive drugs.* Haematuria and bleeding from the umbilicus occurred. (For coagulation studies see Table 1) A blood transfusion was done. Serum urea and creatinin increased and anuria developed. From the 4th—11th day a total of

16 VARIATIONS IN THE CALCIUM FRACTIONS IN PLASMA DURING THE FIRST DAYS OF LIFE

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The study can be divided into three parts:

1) The difference between mother and infant at birth.
2) The variations during the first days of life.
3) The first-day» hypocalcemia with fits.

Total calcium, calcium-fractions, phosphorous and total protein in plasma have been determined in mothers and infants at birth (normal deliveries n=19 sectio cesarean n=10). Blood has been drawn from the mother 5—10 minutes before delivery and from the infant from the umbilical vein at delivery Total calcium (Ca-tot), ultrafiltrable calcium (Ca uf) (which for the most part consists of ionized calcium and to a smaller degree of complexed bound calcium such as phosphate, citrate, sulphate, carbonate) and phosphorous showed significantly higher values for the infant than for the mother The protein bound calcium-fraction (Ca-prot) showed somewhat higher values, but not significantly higher in the mother than in the infant. This can to some extent depend on the significantly higher values for total plasma protein found in the mother

In order to study the decrease of calcium in plasma that develops after birth, a number of infants delivered by sectio cesarean were studied. These infants were selected because of their higher risk of developing a neonatal hypocalcemia with fits (1). Ca tot, Ca-fractions, phosphorous and total protein in plasma were determined during the first days of life. Calcium and phosphorous in the urine were determined during the same period. During the first 6 hours of life there was a decrease in total plasma calcium which for the most part was due to a decrease in the ultrafiltrable calcium-fraction. No certain tendency for the protein-bound calcium-fraction was seen. Some of the infants developed a more marked decrease in Ca-tot and Ca-uf, especially during the second day of life. Their lowest values for Ca-uf at that time ranged from 5 0—5.5 mg per 100 ml plasma. They had no fits. No consistent tendency was observed in the plasma phosphorous and total plasma protein levels. The concentrations of calcium and phosphorous in urine during the first two days of life were negligible.

The mechanism of this neonatal hypocalcemia, also called the first-day hypocalcemia, which develops during the first 48 hours of life is still unknown (1). It is most often seen in. preterm infants, low birth weight infants, infants of mothers with diabetes mellitus and in infants delivered by sectio cesarean, infants born in complicated deliveries (1, 2). In order to investigate whether there exists any borderline for Ca-uf at which the fits start and to investigate the effect of calcium treatment of these fits, a number of infants with this type of hypocalcemia were studied (the presence of hypoglycemia was excluded) The Ca-fractions in plasma were determined before and after treatment with calcium per os. From the results obtained by this study there seems to be a borderline for Ca-uf at 5 0 mg per 100 ml plasma, the fits occurring at values of Ca-uf below this level. The fits disappeared when the value of Ca-uf increased above this borderline. No certain borderline for Ca tot was seen. After an extra amount of calcium per os 1—3 ml Calcium-Sandoz (10 per

Table 1

Week of gestation		Plasminogen %	Antiplasmin %	α_2-macro-globulin %	Inhib of urok. activ of plasm. %	Fibrinogen g/100 ml
< 32	Mean	23.9	91.3	86 1	197 0	0.29
	SD	8.5	21 1	34 1	—	0 18
	N	34	13	14	2	5
33—35	Mean	31 1	81.5	114.5	150	0.28
	SD	9.9	17 4	35 1	—	0.10
	N	35	6	14	3	10
36—38	Mean	34.6	87.2	136.4	199.8	0.26
	SD	11.3	24.8	37 4	—	0 14
	N	37	17	22	5	17
39—42	Mean	37.5	101 0	170.1	188.9	0.23
	SD	14.2	24.8	44.2	58.1	0.10
	N	58	14	27	10	20
> 4..	Mean	72.3	—	183.0	175 0	0.20
	SD	—	—	—	—	—
	N	3	—	2	2	2

includes 29 infants with birthweights appropriate for gestational age

ducts (FSP) in serum and in serum with addition of E aminocaproic acid (EACA) *fibrinogen, plasminogen, antiplasmin, α_2-macroglobulin* inhibitors of urokinase activation of plasminogen. The methods used have been described earlier (1)

Table 1 shows a preliminary computer calculation of the factors of the fibrinolytic system in the total material at various periods of gestation. Plasminogen and α_2-macroglobulin increased significantly while the other factors were at the same levels as in fullterm newborns throughout.

Fibrinolytic activity was demonstrated even in the smallest infants and also in infants which developed IRDS It was high in some infants with severe hypoxia. FSP in serum EACA were studied by serial sampling and were found in infants with severe hypoxia and acidosis. One infant with a large intraventricular haemorrhage showed increasing amounts of FSP speaking in favour of in vivo fibrinolysis.

The investigation is partly a continuation of a study of fibrinolysis in human foetuses (2) It shows that the various factors of the fibrinolytic system are sufficiently developed in preterm infants which are capable of producing fibrinolytic activity The findings argue against the assumption that IRDS is due to a primary deficiency of the fibrinolytic system. It rather lends support to the hypothesis *of an increased fibrinolysis in infants* with hypoxia and acidosis.

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The hp level of newborns with an intrauterine infection was clearly higher than that of normal newborns of the same age. The hp level of infected newborns, aged 0—2 days, was 54.2 ± 33.5 mg/100 ml. The level was highest at the age of one week, 83.8 ± 32.5 mg/100 ml. After that the level decreased and was about 55 mg/100 ml at the age of 3—4 weeks. It is emphasized that individual variations are very high. It is obvious that the hp level is of diagnostic value in newborns with an intrauterine infection.

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18 STUDIES ON HUMAN FOETAL ENDOCRINE PANCREAS IN VITRO

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Explants of pancreas from human foetuses obtained at legal abortions were grown in organ cultures for 2 weeks and the insulin production and the morphology of the islet cells were studied. Eagle's medium with 10 % calf serum and with various levels of glucose (100 300 and 1000 mg per 100 ml) was used and the cultures were exposed continuously to 5 % CO_2 in oxygen. The content of insulin in the media was determined by radioimmunoassay. Preliminary results show a good survival of the β- and α-cells of the islets at the end of the long-term incubation. The insulin level in the media, which was high in the first days of incubation, dropped to lower levels on the seventh through the fourteenth days of culture. It was also noted that the concentration of insulin was higher after growth of cultures in media containing 300 and 1000 mg of glucose per 100 ml than in those containing 100 mg per 100 ml. The results are discussed.

19 EFFECT OF GLUCURONIDES ON THE GLUCURONIDE BIOSYNTHESIS

O. HÄNNINEN and J. MARNIEMI

From the Department of Physiology and Department of Biochemistry, University of Turku, Turku, Finland

The synthesis of glucuronides is catalyzed by UDP glucuronyltransferase(s) bound to the endoplasmic reticulum membranes. The reaction is exergonic and irreversible. The product glucuronides have not, so far been thought to have any effect on the glucuronide biosynthesis.

Phenolphthalein and 1 naphthyl glucur

cent) 3 times per day (= 27—54 mg Ca per day) there was observed after one day an increase of Ca uf over the 5 mg per 100 ml plasma borderline and the fits disappeared.

Possible hypotheses for this type of neonatal hypocalcemia are

I) Decrease of calcium in plasma because of sceletal mineralisation.

II) Thyrocalcitonin response to an increased concentration of ionized calcium existing at birth

An immature parathyroid function might be responsible for the delay in increasing the low plasma calcium level.

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17 HAPTOGLOBIN LEVELS IN NEWBORNS

T T SALMI

From the Children s Hospital and Department of Clinical Chemistry University of Turku Turku Finland

According to earlier investigations carried out by other methods, haptoglobin (hp) occurs in the blood of newborns in very small quantities or not at all (1) Lundh and coworkers (2) have also investigated the hp levels in hemolytic disease of newborns. He observed that the hp level rises to that of adults in exchange transfusion and decreases to a subnormal level in 12 hours.

It has been noted that the hp level is high in adults with an acute or chronic infec tion. Still, there are no investigations as to whether an intrauterine infection has such a strong influence on the hp synthesis that it could cause an increase in the hp level despite the physiological hemolysis of the newborns.

In the present investigation, the hp levels of 140 normal newborns, 60 newborns with an exchange transfusion and 51 newborns with congenital infection (material kindly placed at my disposal by Professor Ossi Pettay Children s Hospital, University of Helsinki) were examined. Hp was determined by a modification of the method presented by Tarukoski (3) This method is accurate at 5—300 mg/100 ml. Free hemoglobin does not make the method inaccurate and thus a hemolytic sample could be examined.

The hp level in a pooled cord blood was determined and it was 8.2 mg/100 ml. In healthy newborns, aged 0—3 days, the level was 26.3 ± 19.9 mg/100 ml. The mean concentration did not change in one month.

The newborns with an exchange transfusion had an average level of 21 4 ± 11.9 mg/100 ml before the transfusion and 82.3 ± 38 1 mg/100 ml after it. The hp level was followed for 1—2 weeks after the exchange transfusion. At the same time the biological half time of hp was determined. The halftime varied greatly in different individuals, ranging from 6 to 30 hours. In some cases the hp level did not decrease at all, which was obviously due to the fact that hemolysis had *stopped because of* the exchange *transfusion.* The half times depending on the indication of the exchange transfusion were compared in the present investigation, but no significant differences were found

During the first week the content of palmitic and arachidonic acids decreased slightly whereas the oleic acid was found to increase.

Somewhat different values were found in infants of low birth weight, where the linolic acid was found to be very low

Related changes in serum levels of vitamin E will be discussed.

21. PARAQUAT INDUCED DERANGEMENT OF PULMONARY SURFACTANT IN THE RAT

B. ROBERTSON G ENHÖRNING B. IVEMARK
EVA MALMQVIST and J MODÉE

From the Department of Paediatric Pathology Karolinska Sjukhuset, Stockholm, Sweden

Female Sprague-Dawley rats (200 g) were injected subcutaneously with 2 per cent aqueous solution of paraquat (dimethyl bipyridylium-dichloride), 35 mg/kg body weight. The animals were sacrificed by intraperitoneal Nembutal at intervals from 2 hours to 7 days after the injection of paraquat. 12 animals served for morphological purposes, whereas alveolar wash was performed in 24 animals. In the latter group, the thoracic viscera were removed *en bloc* and the lungs were washed with 10 cc saline by means of a syringe with its cannula tip just above the carina. The fluid recovered was used for evaluation of surface properties and for determination of phospholipid content.

Respiratory symptoms

Within 12 24 hours after injection of paraquat the animals developed signs of respiratory distress, with increased ventilation rate and intercostal retractions. These symptoms became severe 2—3 days after the injection. In the animals which were allowed to survive 4 days or more, the respiratory symptoms were subsiding.

Morphologic findings

Twelve hours after injection of paraquat, the lungs showed focal atelectasis. This feature became gradually more prominent at subsequent intervals and reached a maximum 2—3 days after injection. Within the atelectatic areas there was overdistension of bronchioles and alveolar ducts, giving to the pulmonary parenchyma a microscopic appearance similar to human atelectasis of prematurity» (Fig. 1 A).

Following the second day after injection of paraquat, there was increasing interstitial inflammation in the lungs, as well as intra-alveolar edema, focal intra-alveolar haemorrhage and scattered hyaline membranes. In the animals killed 7 days after paraquat injection, mural proliferation of cuboidal epithelium was prominent in many peripheral airspaces. (Fig 1 B).

Surface properties of alveolar wash

The surface properties of alveolar wash were evaluated with the pulsating bubble method (1) the principle of which is to record the pressure gradient across the surface of a bubble pulsating in the sample liquid.

onides caused however a 50 % inhibition of o-aminophenyl glucuronide synthesis at 0.5 mM concentrations in rat liver slices, although they did not affect respiration under these conditions. A slow hydrolysis of the glucuronides took place during incubation (0 9 % of phenolphthalein glucuronide added was hydrolyzed in an hour) These glucuronides also inhibited the UDP glucuronyltransferase (p-nitrophenol) of isolated liver microsomal fraction and so did also o-aminophenyl glucuronide The K_I-values were 0 6 and 4 mM for the phenolphthalein and 1 naphthyl glucuronides respectively The free aglycones were also powerful inhibitors of p-nitrophenol conjugation catalyzed by UDP glucuronyl transferase. The K_I-values for phenolphthalein and 1 naphthol were 0 1 and 0 04 mM, respectively 1 Naphthol caused a 50 % inhibition of o-aminophenyl glucuronide synthesis in liver slices at the same concentrat (0 04 mM) as was the K_I-value for UDP g curonyltransferase preparation. p-Nitrophe and o-aminophenol are apparently substra of the same UDP glucuronyltransferase, sł they compete with each other

The results show that glucuronides inhi rather effectively — indicating physiologi significance — the glucuronide biosynthe from phenolic aglycones both in living ce and isolated microsomes. This inhibition not due to the action of free aglycones, though these are slowly released from t glucuronides during incubation.

ACKNOWLEDGEMENT

This study was supported by a grant fr the U.S. Public Health Service (AM-06018-(and from the National Research Council Natural Sciences Finland.

20 CHANGES IN THE LIPID PATTERN OF HUMAN SERA IN THE NEONATAL PERIOD

J CLAUSEN and B FRIIS-HANSEN

From the Neonatal Unit, Department of Paediatrics, University Hospital, Copenhagen, Denmark

The changes in serum beta lipoprotein and the relative distribution of lipoproteins as well as the pattern of fatty acids have been followed in infants during the neonatal period. The data obtained were correlated to the food intake as well as to the growth of the child. In infants living on human milk, the total content of beta-lipoprotein increased from around 30 per cent of the concentration in the mother's serum at birth, to around 80 per cent in the second week of life. During the same period, the lipoprotein pattern changed from a predominance of the pr beta lipoprotein band to a pattern with th beta lipoprotein as a dominating fraction wi contributions from other lipoprotein fractior seen in normal adult sera as elucidated b means of Agar-electrophoresis.

During the same period, the fatty aci pattern also changed. At birth low value of oleic acid and linoleic acid and high value of palmitic acid and arachidonic acid wer found in cord serum as compared to th corresponding values in the mother's blood

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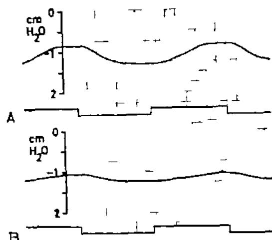


Fig 1 Pressure tracings (after ageing of the *interphase for 10 minutes*) obtained when bubble is pulsating in alveolar wash from control rat (A) and from rat, sacrificed 2 hours after paraquat injection (B). Note the reduction of pressure amplitude in B

of paraquat (3), but also provides quantitative evidence that paraquat influences the surfactant system of the lung Alterations in surface properties of alveolar wash appear already within a few hours after injection of paraquat and precede the development of atelectasis.

The large pressure amplitude observed in tracings from alveolar wash from controls reflects elasticity in the surface layer of the bubble Such elasticity if present in the alveolar lining layer would undoubtedly contribute to the maintenance of mean alveolar size by counteracting the shrinking effect of surface tension. The decrease in pressure amplitude observed in alveolar wash from paraquat-injected rats may therefore explain the development of atelectasis

The derangement of surfactant is possibly due to a disturbance of the phospholipid metabolism of the lung, although this is not reflected in our quantitative determination of total phospholipid P in the alveolar wash. Preliminary results of thin layer chromatography of alveolar wash from the present series revealed a change in the lipid composition of the wash the lecithin fraction disappeared two days after injection of paraquat (unpublished observations)

Conclusion

Our results indicate that derangement of pulmonary surfactant is a pathogenically important factor in the development of the early pulmonary lesions in paraquat poisoning, as suggested by Manktelow (3) This should make paraquat-induced respiratory distress a useful experimental model in further studies concerning pathogenesis and treatment of the idiopathic respiratory distress syndrome, which is related to surfactant deficiency in prematurely born infants.

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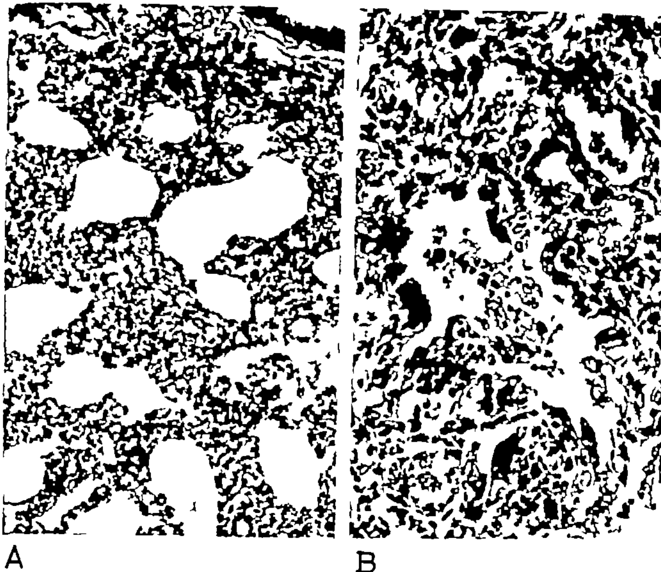


Fig 1 Histologic appearance of the pulmonary parenchyma 2 days (A) and 7 days (B) after injection of paraquat. A. Prominent atelectasis with dilatation of alveolar ducts, a picture similar to human atelectasis of prematurity HE. × 115. B Interstitial pneumonia and mural proliferation of cuboidal epithelium in peripheral airspaces. HE. × 290.

Typical pressure tracings from alveolar wash of control and paraquat injected rats are shown in Fig 2. Tracings from the paraquat injected animals showed a low fluctuation in pressure as compared to the controls. This alteration appeared as early as 2 hours after injection of paraquat and became gradually more prominent at the following intervals.

Phospholipid content of alveolar wash

Lipids were extracted with ethanol-ether (3 1) Total P in the extract was determined photometrically by the p-semidine method, following oxidation of phospholipid P to inorganic phosphate by digestion with H_2SO_4 (30 %) and H_2O_2 (30 %) (2) The result was expressed as mmol P/l.

In the paraquat injected animals, the phospholipid content of alveolar wash varied between 0 12 and 0 44 mmol P/l. There was no significant difference as compared to controls, in which the phospholipid content ranged from 0 16 to 0 46 mmol P/l.

Comment

The present study not only confirms earlier reports on the selective pulmonary toxicity

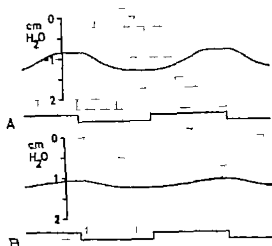


Fig 2. Pressure tracings (after »ageing» of the interphase for 10 minutes) obtained when bubbl is pulsating in alveolar wash from control rat (A) and from rat, sacrificed 3 hours after paraquat injection (B). Note the reduction of pressure amplitude in B.

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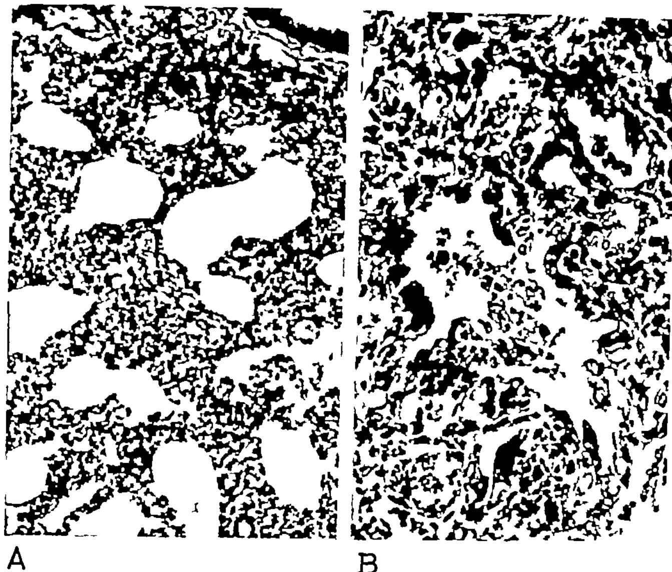


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Comment

The present study not only confirms earlier reports on the selective pulmonary toxicity

malformations can be analyzed and projected against knowledge of the distribution of the teratogen.

Even more important than such retrospective verifications of previously suspected or proved teratogens would be early warning of a population exposed to a »new» teratogen. With sufficient data on the normal occurrence of a certain defect in the population, any rise in its incidence can be detected and its significance calculated.

Registration of all congenital malformations detected in liveborn infants during the first year of life has been compulsory in Finland since 1963.

The actual register was preceded by a retrospective evaluation of the incidence of malformations in the years 1957 to 1962 (Saxén and Härö 1964).

The results of the registration for the years 1963 to 1968 indicate a total of 476.079 births, 5.424 stillbirths and 5.515 congenital malformations. The figure for the incidence of congenital malformations is 1.17 per cent.

In addition, an analysis of factors affecting pregnancy outcome has been made from a selected series, using data for certain defects with a high detection rate and reliable diagnosis. In the years 1964 to 1966 the study group consisted of 344 malformations of the central nervous system and 310 skeletal defects. As 21 of these occurred in the same child, the control group totals 633 healthy infants.

Even if the results are based on a rather small series and the observations are so far only suggestive, a positive correlation was observed between the following factors and an increased risk of congenital malformations.

— maternal age over 30 years
— unmarried mother
— previous stillbirths and abortions
— placental weight below 400 g.
— birth weight below 2.500 g
— influenza during early pregnancy
— malformations in the family

In respect to maternal drug consumption a positive correlation could be established between the use of analgetics and other temporarily used drugs and the frequency of malformations.

Most of these correlations have been noted before and many of them are still not conclusively verified in the present material. They merely illustrate the possible uses of registers of congenital defects, and may suggest some future lines of investigation. In addition they may be useful for the selection of certain risk groups, where even suggestive factors might be valuable.

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24. THE FREQUENCY AND TIME OF DIAGNOSES OF CONGENITAL DEFECTS

J HAKOSALO

From the University of Oulu, Oulu, Finland

SESSION B I

TERATOLOGY

CHAIRMAN LAURI SAXÉN

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22 THE SWEDISH REGISTER OF MALFORMED CHILDREN EXPERIENCES FROM AN EPIDEMIOLOGICAL STUDY

B. KÄLLÉN and J WINBERG

From the Department of Embryology University of Lund, Sweden, and the Department of Paediatrics St. Görans Hospital, Stockholm, Sweden

A national register of congenital malformations covering about 75—80 000 annual births was started on April 1st 1964 by the Swedish National Board of Health. The register was constructed to serve as an early warning system, should a new teratogen become widely spread in the environment. Monthly reports are sent in on children with malformations diagnosed during the neonatal period using special report forms. The experiences with this register up to July 1st, 1969 are reported with special stress on methodological questions. A definite under reporting of some minor malformations can be demonstrated, but major malformations are relatively well reported. Mortality and post mortem rates are shown to be of importance in the control of the accuracy of the reporting The size of the reporting hospital influences the rate of reporting — in some large hospitals a definite under reporting takes place sometimes due to loss of reports on neonatally dead children. The sensitivity of the register is tested and found acceptable. Special stress is laid on the problem of multiple malformations and a mode of analysis is demonstrated, permitting identification of specific »syndromes

23 THE FINNISH REGISTER OF CONGENITAL MALFORMATIONS

Six Years of Experience and Future Plans

ANNELI KLEMETTI and L. SAXÉN

From the National Board of Health, Helsinki Finland

A reliable complete register of congenital malformations can be used for study in two ways when a certain genetic or exogenous factor becomes suspect and has been non-randomly distributed in time or space prevalence figures for all or for some special

malformations can be analysed and projected against knowledge of the distribution of the teratogen.

Even more important than such retrospective verifications of previously suspected or proved teratogens would be early warning of a population exposed to a »new» teratogen. With sufficient data on the normal occurrence of a certain defect in the population, any rise in its incidence can be detected and its significance calculated.

Registration of all congenital malformations detected in liveborn infants during the first year of life has been compulsory in Finland since 1963.

The actual register was preceded by a retrospective evaluation of the incidence of malformations in the years 1957 to 1962 (Saxén and Härö 1964).

The results of the registration for the years 1963 to 1968 indicate a total of 476.079 births, 5.428 stillbirths and 5.515 congenital malformations. The figure for the incidence of congenital malformations is 1.17 per cent.

In addition, an analysis of factors affecting pregnancy outcome has been made from a selected series, using data for certain defects with a high detection rate and reliable diagnosis. In the years 1964 to 1966 the study group consisted of 344 malformations of the central nervous system and 310 skeletal defects. As 21 of these occurred in the same child, the control group totals 833 healthy infants.

Even if the results are based on a rather small series and the observations are so far only suggestive a positive correlation was observed between the following factors and an increased risk of congenital malformations.

— maternal age over 30 years
— unmarried mother
— previous stillbirths and abortions
— placental weight below 400 g.
— birth weight below 2.500 g
— influenza during early pregnancy
— malformations in the family

In respect to maternal drug consumption a positive correlation could be established between the use of analgetics and other temporarily used drugs and the frequency of malformations.

Most of these correlations have been noted before and many of them are still not conclusively verified in the present material. They merely illustrate the possible uses of registers of congenital defects, and may suggest some future lines of investigation. In addition they may be useful for the selection of certain risk groups, where even suggestive factors might be valuable.

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24. THE FREQUENCY AND TIME OF DIAGNOSES OF CONGENITAL DEFECTS

J HAKOSALO

From the University of Oulu, Oulu, Finland

25 CONGENITAL HEART MALFORMATIONS IN AN AUTOPSY MATERIAL

B. LANDTMAN and J RAPOLA

From the Children s Hospital, University of Helsinki Helsinki, Finland

26 THE ETIOLOGY OF PATENT DUCTUS ARTERIOSUS

P ZETTERQVIST

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In order to study the role of genetic factors in the etiology of patent ductus arteriosus the author has traced all Swedish citizens born 1945 or earlier who have been operated upon for this type of CHD at the departments for heart surgery in Stockholm during the years 1941—1965 Up to the time of study (1967—1969) 491 children of such probands had been born and survived the neonatal period Among these children there were encountered 14 cases of isolated PDA and one case of PDA with associated coarctation of the aorta (in one of a couple of identical male twins)

The incidence in children of affected individuals is of the same order as generally found in subsequent sibs of probands. It corresponds to the square root of the incid ence among unselected newborn babies, which is estimated at about 0 8 per 1 000 These facts support the hypothesis of multi factorial inheritance The heritability ac cording to Falconer is estimated at about 70 %.

The concept of multifactorial inheritance includes the possible role of factors other than mutant genes. Environmental factors as well as variations in the karyotype, includ ing the normal chromosomal difference be- tween the two sexes may be of significance. This is in accordance with what is known about PDA and also conforms to the present view on the etiology of malformations in general.

What has been said here does not by any means imply that every case of PDA is a true malformation from a pathogenetic point of view i.e an immediate result of an abnormal process of organogenesis Perhaps it would be more appropriate to look upon this lesion as a result of a disturbance of the postnatal circulatory adaptation with varia tions from one case to another as regards etiology and pathogenesis. In contrast with typical malformations the lesion may occa sionally be due to environmental factors act ing during the fetal stage or to a heritable disorder of connective tissue.

Peri and postnatal environmental factors such as low oxygen tension and disturbances in production, transport, or effect of cathe- colamines have also been incriminated, but the role of these factors has not been assessed.

The rate of occurrence of congenital heart diseases other than PDA, 2 or perhaps 3 cases, in the present series corresponds to the incidence among newborns in general.

All 14 cases of isolated PDA have been successfully operated on.

27 EXPERIMENTALLY INDUCED HYDRAMNION IN RATS AN ANIMAL MODEL

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Although the reported incidences differ widely there is a known association between the occurrence of hydramnion in women and open defects of the foetal central nervous system such as anencephaly anomalies of the digestive tract, homozygotic twinning, chorio-angiomas of the placenta, and an increased perinatal mortality Open defects of the foetal nervous system and cleft palate can readily be induced in laboratory rodents and a few observations on associated hydramnion have been reported (2,3) Clomiphene-induced hydramnion without such associated defects may prove to be an useful animal model for the study of hydramnion. The present report is a survey of our work to date.

MATERIAL AND METHODS

Pertinent details concerning time, manner and amount of Clomiphene citrate treatment can be found in Table 1 Full details will be published elsewhere (1)

RESULTS

The results in Table 1 demonstrate that Clomiphene in a single dose can induce hydramnion as measured in rat foetuses obtained by hysterotomy on the 20th day of gestation. The effect was statistically significant even after treatment as early as the 6th day i.e. immediately post implantation and in doses from 2 mg/kg maternal body weight.

Table 1. *Weight of foetal fluid (g mean ± S.E) from living rat foetuses after a single subcutaneous injection of Clomiphene. All foetuses examined on 20th day of gestation.*

Dose 1 / Gestation Day	2 mg/kg	10 mg/kg	50 mg/kg	200 mg/kg
6th	0.806 ± 0.017 *** n = 37	0.830 ± 0.021 *** n = 40	0.861 ± 0.056 n = 38	1.476 ± 0.035 *** n = 26
8th	0.792 ± 0.053 n = 36	0.825 ± 0.022 *** n = 34	1.171 ± 0.127 *** n = 19	0.946 ± 0.051 *** n = 14
10th	0.778 ± 0.012 *** n = 44	0.764 ± 0.015 ** n = 50	0.759 ± 0.024 n = 37	0.828 ± 0.047 n = 30
12th	0.803 ± 0.009 *** n = 46	0.838 ± 0.016 *** n = 77	0.828 ± 0.018 *** n = 86	0.878 ± 0.016 *** n = 212
14th				0.746 ± 0.014 n = 74
16th				0.806 ± 0.011 *** n = 62

Weight of foetal fluid for accumulated control foetuses 0.728 ± 0.006 g, n = 478.
(comparison with accumulated controls)

* = $P < 0.05$
** = $P < 0.01$
*** = $P < 0.001$

At all dose levels and times (except the 14th and 16th day) significantly ($P < 0.05$) lighter foetuses were obtained. The difference between control and test groups did not exceed 22 per cent (≈ 0.5 g)

Placental wet weights did not have a uniform trend Thus placentas from animals receiving Clomiphene (2—200 mg/kg) on the 6th day were significantly ($P < 0.001$) heavier and those given Clomiphene on the 12th day were significantly ($P < 0.001$) lighter than the accumulated controls.

Foetal mortality was heaviest among the litters exposed in the 8th day and to higher doses up to 80 per cent of all implantations in the 200 mg group compared with 6 per cent for the accumulated control litters

There were no examples of palatoschisis among the control foetuses. With a single exception, palatoschisis was limited to the 200 mg litters with about 10 per cent of the foetuses involved. No examples of oesophageal or intestinal anomalies were present among the 40 foetuses from the 12th day/200 mg group examined in detail in this respect.

Congenital cataracts were absent in the 2 mg group but present in 3 of the 128 examined foetuses of the 10 mg group and in 17—61 per cent of the 50 and 200 mg groups. The only other ocular anomalies observed were a few colobomas among the 6th and 8th day groups (50—200 mg/kg)

COMMENT

The induction of hydramnion of the magnitude reported here, but not of the other defects tested for by a 2 mg/kg dose of Clomiphene in the 6th day of gestation, implies that Clomiphene primarily affects the formation and/or transfer of foetal fluid. However the mechanism governing this process remains unknown but our present work represents a quantification of the effect, thus facilitating further studies of hydramnion in a suitable animal model.

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Key words
Hydramnion, rat, Clomiphene

28 STUDIES ON THE INHIBITORY EFFECT OF TETRACYCLINE ON OSTEOGENESIS IN VITRO

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From the Laboratory of Experimental Embryology Third Department of Pathology and Children's Hospital, University of Helsinki, Helsinki, Finland

Tetracycline in low concentration was shown to inhibit mineralization of mouse embryonic bones grown in organ cultures. This effect was determined by measuring the elongation of the calcified diaphysis, the increase of total calcium and the uptake of ^{45}Ca of the bones

cultured in a chemically defined medium. In a tenfold concentration tetracycline depressed bone matrix formation, determined by the effect on collagen biosynthesis. Significantly higher concentrations were needed to interfere with DNA synthesis in the bone cells.

The effects of tetracycline on matrix formation and on mineralization were separated by depressing the collagen biosynthesis by cycloheximide and by cyanide no subsequent inhibition of mineralization could be observed.

The results support the view that the clinically and experimentally observed adverse effects of tetracycline on teeth formation and on skeletal growth are induced by a direct action on primary nucleation and/or crystal growth of bone salts during the mineralization process. Hence, further studies are in progress using mineralization of reconstituted collagen fibres in vitro as a model system.

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SESSION C I

CARDIOLOGY

CHAIRMEN MAGNUS MICHAËLSSON and LARS-ERIK CARLGREN

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29 ELECTROCARDIOGRAPHIC STUDIES DURING AND AFTER DELIVERY

I Preliminary Report

H. WENDEL and D E. WIKLUND

From the Department of Obstetrics & Gynecology and Paediatrics University of Umeå Umeå Sweden

The hours during delivery and immediately afterwards are the most hazardous part of our life In spite of all efforts to reduce perinatal mortality more deaths occur during this period than from all causes in the next four decades. Every year a number of mature and apparently healthy fetuses die from intrapartum fetal distress.

During the last decades the interest of both obstetricians and paediatricians has focused on this short but high risk journey Several methods for monitoring the fetus have been developed. Studies in this field are a complicated matter as there is no general agreement as to how to define a normal fetus and fetal distress. According to Beard (1) the term fetal distress refers to the state in which there is a metabolic as well as a circulatory response to hypoxia, which if prolonged results in neurological damage or death of the fetus. The fetus becomes hypoxic either because of inadequate uteroplacental exhange or because of com pression of the umbilical cord.

The newborn with fetal distress will often show postnatal complications, either acute neonatal asphyxia or severe respiratory distress as IRDS or aspiration syndrome depending on its gestational age.

The best way to supervise the fetus during labour seems to be to continuously monitor the fetal heart rate in relation to the intrauterine pressure If the pattern characteristic of asphyxia develops, the acid-base balance of the fetus should be estimated. The available data from this situation are somewhat conflicting The aim of the present study was to relate the fetal heart rate fetal ECG to the time-axis of labour and to correlate these findings with the acid-base balance and ECG of the newborn infant. We have used Hon s electrode for continuous recording of the fetal heart rate Sometimes a pair of intracutaneous suction electrodes (2) were used, one attached transcervically to the back of the fetus and the other to the presenting part of the fetus. The earth lead was connected to the mother The data were recorded on a directwriting jet recorder (Mingograph 8 OB) with specially designer

preamplifier The paper speed was usually 50 mm/sec. The uterine pressure was roughly estimated manually

Immediately after delivery before clamping of the cord and usually before the first breath, two samples of blood were collected from the umbilical vein, one of them in a 5 ml heparinized glass syringe for acid-base balance determination. The sample was stored at 4 C and analyses were performed within 30 minutes, using a thermostated Radiometer Blood Micro System BMS 3 b and a Digital Acid-base Analyzer PHM 72 or Radiometer PHM 27 The other blood sample was used to estimate Na, K and Cl (Technicon Auto-Analyzer), Ca (Eppendorf photometer) and Mg (Zeiss Spectrophotometer PHQ II) Hemoglob n and hematocrit estimations were also performed.

By now 35 parturients have been studied nd the infants followed by electrocardiorams during the first five days after birth. he deceleration patterns obtained by other rorkers in this field were confirmed. A rofound deceleration pattern with a fetal heart rate of 30—60 beats per minute was noted in most cases during the second stage a pattern not found reported in the literature. In all these cases the infants were vital with acid-base balance in the normal range and Apgar scores above 7 points after one and ten minutes. In a few cases the ventricular complex was notched, perhaps due to fetal acidosis according to Pardi et al. (3)

The material is still not statistically analyzed with respect to the relation of the fetal heart rate or of the different ECG complexes to the time-axis or acid-base balance.

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30 CARDIORESPIRATORY STUDIES ON NEONATAL LAMBS DURING HYPOTHERMIA

E. LÄNSIMIES, J KLOSSNER and A. KOIVIKKO

From the Cardiorespiratory Research Unit and the Children' Hospital University of Turku, Turku, Finland

It has been reported that the oxygen consumption and cardiovascular funtions of non-shivering neonatal lambs change in a way essentially similar to those of adult mammals during hypothermia.

T confirm these findings we relaxed chloralose-anaesthetized lambs with pancuronium to suppress shivering during hypothermia. Another group of lambs was given chloralose and was allowed to shiver during cooling in a ice-water bath. Th lambs were 2 to 7 days old. Aortic and pulmonary arterial pressures, heart rate, dye dilution curves, oxygen consumption and body temperature were registered. Arterial blood samples were taken for measurements of acid-base balance and oxygen saturation values.

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Since this method has proved suitable for a more detailed analysis of the central circulatory system in the adult its application in the neonatal period has been attempted.

METHOD

Approximately 10 microcuri of Technicium — 99 m — albumin in saline are injected as a bolus in the inferior caval vein by means of catheter (feeding tube French size 8) inserted via the umbilical vein the activity is recorded precordially using specially designed collimator and multichannel analyzer

As judged from the pulse reaction recorded electrocardiographically the injection (total volume 2—3 ml) does not noticeably interfere with the central hemodynamics. For the determination of blood volume approximately 0.1 microcuri of J — 125 — albumin is then injected by the same route, blood samples are taken after mixing period of 5 minutes with catheter (feeding tube French size 8) inserted in one of the umbilical arteries and analyzed by means of a well crystal detector With 10 microcuri of T — 99 m, the whole body radiation dose is below 4 mrad.

PRELIMINARY RESULTS

Results obtained in 5 newborn infants without major cardio-pulmonary problems are given in Table 1 Only in two of them was the blood volume simultaneously determined. Compared with typical adult values (LHV = 5.2 ± 1.1 /₀, RHV = 4.8 ± 0.3 / of total blood volume) both the relative left and right heart volumes are larger which corresponds well to the newborn's bigger heart volume as determined radiographically The somewhat bigger left heart volume in the younger age group (cases 2, 3 4, 5) is consistent with a L—R shunt through the ductus arteriosus which affects exclusively the circulating blood volume in the pulmonary circulation, the left heart and the initial part of the aorta. The relative pulmonary blood volume seems to be smaller than in the adult (8.0 ± 1.1 of TBV)

Table 1

No, Sex	Birth Weight g	Age hrs	Total Blood Vol ml	Cardiac Output ml/min	CO/TBV min-1	Right Heart Blood Vol ml	Right Heart Blood Vol / of TBV	Left Heart Blood Vol ml	Left Heart Blood Vol / of TBV	Pulm. Transit Time sec	Pulm. Blood V l ml	Pulm. Blood V l / of TBV
1 F	2,740	8			2.8		9.0		8.3	1.0		
		8 15			2.5		8.3		8.0	1.0		
2 M	4,600	1			2.6		7.0		6.8	1.0		
3 F	3,560	1			2.0		6.6		10.8	1.2		
4 F	3,520	2.5	340	990	2.9	23	6.9	25	7.4	1.0	16	5.4
5 F	3,400	3	240	660	2.8	15	6.3	20	8.3	1.3	16	6.6

The oxygen consumption, cardiac output, heart rate and stroke volume of the non shivering animals decreased in agreement with the earlier findings. The results for the shivering lambs were quite different. The oxygen consumptions increased even three- fold or remained at the initial level. A remarkable decrease of the oxygen con sumption was first observed below 29°C The cardiac outputs of the shivering lambs increased roughly parallel to the increases of oxygen consumption. The authors feel that decreasing levels of standard bicarbonate suppressed the increase of the cardiac output. The increased cardiac outputs of lambs with increased oxygen consumption were effected almost completely by increases of the stroke volume the heart rates of these lambs decreased roughly in the same range as those of non-shivering lambs.

The cardiorespiratory changes of neonatal lambs during hypothermia with or without shivering are essentially similar to those observed for adult mammals. The failure of the heart rate response to contribute to the increase of cardiac output during shivering is an interesting finding and will require more investigation.

This work was supported by a grant from Yrjö Jahnsson Foundation which is gratefully acknowledged.

31 DETERMINATION OF CARDIAC AND PULMONARY BLOOD VOLUMES AND CARDIAC OUTPUT IN THE NEONATAL PERIOD BY MEANS OF RADIOISOTOPE DILUTION CURVES

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INTRODUCTION

Radioisotope dilution curves (radiocardiograms) recorded externally have been used during the last few years for detection of cardiac shunts as an adjunct to cardiac catheterization in adults (2) An analog computer program for the analysis of such radioisotope curves, recently described by one of use (1) provides the possibility for a quantitative determination of the pulmonary blood volume (PBV) the volumes of the heart chambers and the pulmonary transit time If the total blood volume (TBV) is known, cardiac output can be calculated. The analysis is based on the principle of fitting the radiocardiogram recorded to the analog model by varying the parameters of the model, i.e the potentiometer values of the computer in such a way that the radiocardiogram thus produced closely corresponds to the one recorded. The effect of different cardiac functional defects on the radiocardiogram can also be simulated by the analog computer Since the activity in the atrium and in the ventricle affects the form of the radioisotope dilution curve almost equally there is some uncertainty in the differentiation of the atrium and ventricle by computer analysis. Therefore only the total volume of the right and the left heart is calculated (RHV LHV).

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METHOD

Approximately 10 microcuri of Technicium — 99 m — albumin in saline are injected as a bolus in the inferior caval vein by means of a catheter (feeding tube French size 8) inserted via the umbilical vein, the activity is recorded precordially using a specially designed collimator and a multichannel analyzer

As judged from the pulse reaction recorded electrocardiographically the injection (total vol ume 2—3 ml) does not noticeably interfere with the central hemodynamics. For the determination of blood volume approximately 0 1 microcuri of J — 125 — albumin is then injected by the same route, blood samples are taken after mixing period of 5 minutes with catheter (feeding tube French size 8) inserted in one of the umbilical arteries and analyzed by means of well cristal detector. With 10 microcuri of T — 99 m, the whole body radiation dose is below 4 mrad

PRELIMINARY RESULTS

Results obtained in 5 newborn infants without major cardio-pulmonary problems are given in Table 1. Only in two of them was the blood volume simultaneously determined. Compared with typical adult values (LHV = 5.2 ± 1.1 /₀, RHV = 4.8 ± 0.3 % of total blood volume) both the relative left and right heart volumes are larger which corresponds well to the newborn s bigger heart volume as determined radiographically The somewhat bigger left heart volume in the younger age group (cases 2, 3, 4, 5) is consistent with a L—R shunt through the ductus arteriosus which affects exclusively the circulating blood volume in the pulmonary circulation, the left heart and the initial part of the aorta. The relative pulmonary blood volume seems to be smaller than in the adult (8.0 ± 1.1 of TBV)

4

Table 1

No, Sex	Birth Weight gm	Age hrs	Total Blood Vol. ml	Cardiac Output ml/min	CO/TBV min 1	Right Heart Blood Vol. ml	/ of TBV	Left Heart Blood Vol. ml	/ of TBV	Pulm. Transit Time sec	Pulm. Blood Vol. ml	/ f TBV
1 F	2,740	8			2.6		9.0		8.8	1.0		
		8 15			2.5		8.3		8.0	1.0		
2 M	4,000	1			2.6		7.0		8.8	1.0		
3 F	3,660	1			3.0		6.8		10.8	1.2		
4 F	3,620	2.5	340	990	2.9	23	8.9	23	7.4	1.0	18	8.4
5 F	2,400	3	240	660	2.8	15	6.3	20	8.3	1.3	16	6.6

The right ventricular cardiac output determined from the TBV and the mean circulation time T as C. O = TBV/T appears to be somewhat higher than that estimated by means of other methods.

The accuracy of the results is dependent upon the measuring statistics. Experience so far obtained seems to indicate that very small shunts (below 10—20 per cent of C. O) are not detectable even in the presence of good measuring statistics.

With further experience this technique may prove a suitable method for obtaining a more detailed analysis of some relevant circulatory parameters in the newborn infant.

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32. THERMODILUTION TECHNIQUE FOR THE QUANTITATION OF INTRA-CARDIAC SHUNTS AN EXPERIMENTAL EVALUATION

GUNNEL HEDVALL, I. KJELLMER and T OLSSON

From the Department of Paediatrics, University of Gothenburg and Research Laboratory of Medical Electronics Chalmers University of Technology Gothenburg Sweden

Indicator dilution methods have been used extensively for demonstration of existence and direction of intra-cardiac shunts. However no ideal method exists for the quantitative determination of blood flow through such shunts Several different ways to analyse the indicator dilution curves graphically have been suggested for this purpose. Most described methods, however do not appear to have been tested against a reliable independent method. Therefore it was considered necessary to create a model situation that allowed the simultaneous recording of cardiac output and shunt blood flow with a reference method and the recording of indicator dilution curves. The thermodilution technique was used, as this seemed to be the method most easily applied in a clinical situation working with babies.

Adult cats were used. Two situations were simulated 1) a right to-left shunt through the foramen ovale (shunt connecting the two atria and shunt flow varied by means of a graded constriction of the pulmonary artery), and 2) a left to-right shunt through the ductus arteriosus (shunt connecting the aorta and pulmonary artery and shunt flow varied by means of a graded constriction of the shunt tubing) The actual flow through the aortic root and the shunt was measured with electromagnetic flow probes. The detecting thermistor was introduced in the abdominal aorta on the tip of a catheter passed from a peripheral artery Injections of saline at room temperature were performed via catheters in the right and left atria. The resulting thermodilution curves were analyzed using two methods. The R—L shunt curves were in most cases evaluated with the forward triangle method according to

Swan et al. (1) while the L—R shunt curves were analyzed as described by Mook and Zijlstra (2) by the monoexponential extrapolation of the downslope both of the primary and the shunt curves. The shunt flow expressed as a fraction of aortic or pulmonary blood flow was then calculated. These values were compared with those obtained by the reference method. The use of the forward triangle method was limited to shunts below 60 per cent of cardiac output because of the poor delineation of the peak of the primary curve at higher shunt fractions. The results obtained from the thermodilution curves were correlated to the reference values with a high degree of statistical significance. The methodological error however was large for both types of shunts, being higher for the L—R than for the R—L shunts.

The magnitude of the R—L shunts was also calculated from blood gas data. The results obtained by the thermodilution method were significantly better correlated to the reference values than those calculated from the blood gas equation.

It is concluded that the graphical analysis of thermodilution curves allows the estimation of the magnitude of intra-cardiac shunts. Great caution must however be exercised in the interpretation of such data because of considerable methodological errors.

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33. NATURAL HISTORY OF CONGENITAL AORTIC STENOSIS

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134 cases of isolated congenital aortic stenosis were seen among approximately 5000 cases of congenital heart disease studied from 1950 to 1969 (2.4 %). There were 82 boys and 52 girls.

The diagnosis was in most cases based on the characteristic clinical findings.

The follow up time was in 50 % of the cases more than 5 years. The age of the patient at the last examination was over 10 years in two thirds of the cases. Twelve patients, six of them less than fifteen years old, were operated on and excluded from the study.

Seven of the patients died during the first year of life. After this age, however very few children seemed to suffer from their aortic stenosis. The growth of the children was not retarded. 75 % of all patients were asymptomatic at their last examination. An increase of disability and symptoms occurred with age. 33 patients had a pulse pressure of 25 mm Hg or less. As a group they did not have more symptoms or worse prognosis than those with a normal pulse pressure.

In the X ray a prominent left ventricle and ascending aorta were seen in most cases. Cardiomegaly mostly slight, was observed in 27 cases. Marked cardiomegaly was only seen in connection with heart failure or significant aortic regurgitation.

43 patients had normal electrocardiograms at their last examination. Left ventricular hypertrophy by the voltage was present in

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The accuracy of the results is dependent upon the measuring statistics. Experience so far obtained seems to indicate that very small shunts (below 10—20 per cent of C. O) are not detectable even in the presence of good measuring statistics.

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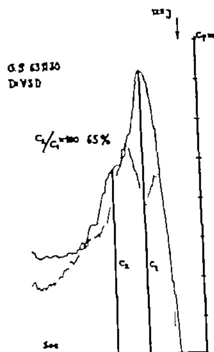


Fig. 1 Curves obtained from patient with VSD. The upper curve is registed by the pulmonary detector and the lower doubl peaked curve by the precordial detector

detector after the activity from the right ventricle and before the activity from the left ventricle (Fig. 1). Furthermore, it is necessary with a narrowly collimated detector when using a high energetic isotope as Technetium-99m. In some patients repeated injections with different localization of the detectors were necessary to obtain representative curves. ^{131}J Na-Hippurate, which is rapidly excreted through the kidneys, is therefore preferred to Technetium-99m.

It was found that in patients with no signs of left-to-right shunts the C_2/C_1 ratio was less than 40 /. In patients with small shunts (i.e. lung flow/systemic flow less than 2/1) the ratio was between 40 and 60 / and in patients with large shunts more than 60 /.

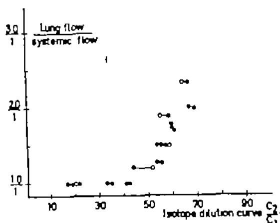


Fig. 2. Relationship between pulmonary flow/systemic flow calculated from oxygen saturation data and the C_2/C_1 ratio.

● patients investigated with ^{131}J

●——o patients investigated with ^{131}J and ^{99}Tc^{m}

In small shunts there is a good correlation between pulmonary flow/systemic flow calculated from oxygen saturation data and the C_2/C_1 ratio (Fig 2).

The described technique is simple and can easily be repeated. It should therefore be valuable during childhood in screening patients with moderate heart enlargement and/or murmurs suggesting left to-right shunts and in follow up studies of patients with left to-right shunts. Even in other clinical situations e.g. in control of patients in the immediate postoperative period or later after surgical correction of heart lesions with left-to-right shunt the method should be of great value.

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64 cases and left ventricular strain in 27 cases. There were fifteen patients who developed left ventricular strain during the follow up having at first had only left ventricular hypertrophy

There were eighteen fatalities during the follow up Seven infants all having a severe valvular stenosis, died at the age of 2 days to eight months In all congestive heart failure was present and was probably the main cause of death.

Seven patients died at the age of 3 to 15 years and 4 patients at 15 to 22 years. In two early cases subacute bacterial endocar ditis and in three cases heart failure was the cause of death.

Six patients died suddenly 4 of them w more than 15 years old. Only one of patients was asymptomatic. One boy o years of age had no disability but had two episodes of syncope after exer All the others complained of fatigability dyspnea on exertion. The electrocardiog showed left ventricular hypertrophy in cases, but moderate or marked ST—T char were recorded in only two cases.

The incidence of sudden death in the wh series was 4 % and in those less than 15 ye 1.5 % No asymptomatic child and no ch without left ventricular hypertrophy in electrocardiogram died before the age fifteen.

34 EXTERNAL DETECTION OF RADIOISOTOPES IN QUANTITATION OF CARDIAC LEFT TO-RIGHT SHUNTS

H. AHLSTRÖM

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The use of radioactive isotopes in the diag nosis of cardiac left to-right shunts has been practised for several years. If a radio-isotope is injected into a peripheral vein and a scintillation detector is placed over the precordium, even very small shunts can be detected. By recording pulmonary vascular dilution curves Folse and Braunwald (1) simplified the method.

The aim of this study was to achieve quantitative information as to the magnitude of the shunts. The studies were performed during or immediately after cardiac catheter ization. A scintillation detector was placed over an apical lung field, and the peak activi ty (C_1) and the activity after one build up time (C_2) were measured (Fig 1) Oxygen sa turation data were utilized in quantitation of the shunt during the catheterization. T calculated ratio pulmonary flow/systen flow was compared with the ratio of activi C_2 to C_1 expressed as a percentage. Tv radioisotopes were utilized, [125]J Na Hi purate and Technetium-99m. With different collimated detectors the two isotopes we found to be equivalent in quantitation the shunts. It is, however important th the detector only registers activity from lu flow and not activity from the heart ar the systemic circulation. During the invest gation it was found that another detecto placed over the precordium, was necessar This detector registers a double peaked curv representing activity from the right and th left ventricles. The maximal activity fror the lung must be obtained by the lun

with the probability of 95 per cent, and in the same way the preoperative weight of the girls was somewhat better than that of the boys, but the difference was not statistically significant. One year after operation the average height and weight of the girls were better than those of the boys with the probability of 95 per cent.

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

This group comprised 42 girls and 13 boys.

The average preoperative height and weight of the girls were statistically lower than the normal with the probability of 99.95 per cent. The average postoperative height was statistically lower than normal with the probability of 99.5 per cent and the weight with 99.95 per cent.

The average preoperative height and weight of the boys were statistically lower than normal with the probability of 99 per cent. The average postoperative height was lower than the normal with the probability of 95 per cent and the weight with 97.5 per cent.

Before operation both the average height and weight of the girls were lower than those of the boys, but the differences were not statistically significant. After operation the increase of the height and weight of the girls was better and so after operation both the average height and weight of the girls were higher than those of the boys, but the differences were still not statistically significant.

CONCLUSION

Between the different groups there were significant differences both before and after operation.

The patients were divided into three groups according to their age at the time of operation those under 7 those between 7 and 10 and those over 11. The postoperative increase in height and weight was the best in the youngest children in every group.

36. REGIONAL LUNG FUNCTION IN CONGENITAL MALFORMATIONS OF THE PULMONARY ARTERIES

M. ARBORELIUS J B KJELLMAN N R. LUNDSTRÖM, W MORTENSSON and Y NAVERSTEN

From the Department of Clinical Physiology Malmö, Departments of Paediatrics, Radiology and Radiation Physics, Lund, Sweden

Absence or hypoplasia of a major branch o stenosis of central branches of the pulmonary artery are malformations which commonly result in reduced blood flow to various parts of the lung.

The prognosis is often good but various complications may sometimes require surgical treatment.

Estimations of the regional lung function would be important in the preoperative evaluation of these patients.

In this preliminary communication the results of estimation of the regional lung function in three patients with different kinds of pulmonary artery malformations will be given and discussed.

METHODS

Regional lung function was estimated with two methods a) ^{133}Xe-radiospirometry using ^{133}Xe and eight paired, fixed detectors (3, 4). With this method the ventilation during normal breathing,

35 PHYSICAL DEVELOPMENT OF CHILDREN WITH CONGENITAL HEART DISEASE

PIRKKO SUONINEN

From the Children's Hospital, University of Helsinki, Helsinki, Finland

The physical developmental pattern of children with different forms of congenital heart disease was studied before and after cardiac surgery The series comprised 100 cases of typical patent ductus arteriosus, 100 cases of coarctation of the aorta, 100 cases of Fallot's tetralogy and 55 cases of patent ductus arteriosus with pulmonary hypertension. The height and weight of the children were correlated with the nature and severity of the heart disease, physical capacity electrocardiogram, cardiomegaly heart failure and hematological data. The collected data were analyzed by means of a computer

In this paper only the average height and weight before and about one year after surgery will be presented

PATENT DUCTUS ARTERIOSUS

This group comprised 73 girls and 27 boys. The physical development of the girls showed statistically subnormal values the probability being 99 per cent for the height and 99.95 per cent for the weight. One year after operation neither of them differed statistically from the normal any more.

The average preoperative height and weight of the boys differed statistically from the normal with the probability of 99 5 per cent. One year after operation the height still differed statistically with the probability of 97.5 per cent from the normal, whereas the average weight did not differ from the normal. The average height and weight of the girls showed higher values before and after operation than those of the boys, but only the height was statistically significantly greater one year after operation

COARCTATION OF THE AORTA

There were 22 girls and 78 boys in this group The average preoperative height and weight of the girls were statistically lower than normal with the probability of 95 per cent. The average postoperative height and weight did not differ significantly from the normal.

The average preoperative height of the boys was statistically lower than normal with the probability of 97.5 per cent and the weight with the probability of 99 per cent. One year after operation the average height and weight did not significantly differ from normal values.

The height and weight of the girls were both before and after operation lower than those of the boys, but the differences were not significant.

TETRALOGY OF FALLOT

This group comprised 38 girls and 62 boys on whom a palliative operation had been performed.

The average preoperative height of the girls was statistically with the probability of 99.5 per cent and the weight of 99 95 per cent lower than the normal. One year after the palliative operation the average height was with the probability of 95 per cent and the weight of 99.95 per cent statistically lower than the normal.

The average preoperative and postoperative height and weight of the boys were statistically lower than normal standards with the probability of 99.95 per cent.

The preoperative height of the girls was statistically better than that of the boys,

with the probability of 95 per cent, and in the same way the preoperative weight of the girls was somewhat better than that of the boys, but the difference was not statistically significant. One year after operation the average height and weight of the girls were better than those of the boys with the probability of 95 per cent.

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The average preoperative and postopera tive height and weight of the boys were statistically lower than normal standards with the probability of 99.95 per cent.

The preoperative height of the girls was statistically better than that of the boys,

are concerned, since a long follow-up of the patients requires not only studies of the deformity but also of the very dynamic development from child to adult. Also very little is known about the natural history of funnel chest. Here thorough prospective studies are needed. But it must be stressed that it is almost impossible to find controls with the same physical constitution as is usual among individuals with funnel chest and who fulfil other criteria for acceptable controls.

In the study presented here we have followed a group of patients with funnel chest for 10—15 years in order to be able to evaluate the effect of surgical correction. A careful examination including heart catheterization, angiocardiography transversal tomography and ventilation capacity studies was performed before the operation. Some parents refused operation. Thus we have a control group prospectively judged in the same way as the operated cases.

The criteria for our index patients have been that by the time of the present examination they were at least 18 years old and had their operation or first investigation per formed more than ten years ago. We have collected 37 operated and 38 not operated cases, who have all been subjected to new careful examinations. Each case has been compared with matched controls of the same sex without chest deformity and born at the same date.

Our material shows that funnel chest has no tendency to increase with age

Transversal tomography is the best method to evaluate the room-restricting effect of the deformity An X-ray in side projec tion gives about the same result, as the best measurement is the distance between the vertebral column and the back conture of the heart. The depth of the funnel is of little interest. Many patients have a very thin thorax. In these individuals a shallow funnel may fill out more of the thoracic cavity than a deeper funnel in a wide chest.

The examinations of heart function, lung volumes and ventilation capacity do not show any significant difference between operated and not operated patients. Operated individuals show a slight reduction of ventilatory capacity as a sign of less elasticity in the chest wall. Funnel chest patients are taller and thinner than the controls and may possibly have a somewhat lower working capacity than the controls.

The operative method has in most cases been a modification of Brown s method with a rib inserted behind the sternum.

38. OBSTRUCTIVE ANOMALIES IN THE PULMONARY VEINS OR THE LEFT ATRIUM CAUSING HEART FAILURE DURING THE FIRST YEAR

N R. LUNDSTRÖM and W MORTENSSON

From the Department of Paediatrics and Department of Radiology, University Hospital, Lund, Sweden

Congenital malformations with obstruction [o]f pulmonary venous return or blood flow through the left atrium often cause symptoms during the first year of life. The following malformations will be discussed 1) Stenosis or atresia of one or several pulmonary veins which drain into the left atrium. 2) Stenosis of a persistent common pulmonary vein. 3)

the vital capacity the perfusion and the volume of each lung and its apical and basal fields can be estimated.

b) ^{131}I MAA scintigraphy using injection of ^{131}I labelled macroaggregated albumin and a Picker Magna Scanner V (1) In one patient (case 3) the information was also digitalized and punched on paper tape simultaneously with the scan and processed in a computer (2)

MATERIAL

1 Girl, 15 years of age, with absence of the right main branch of the pulmonary artery

2 *Girl 10 years of age with hypoplasia of* the right main branch of the pulmonary artery and its two first branches.

3 Boy 19 years of age, with bilateral central and peripheral constrictions of the pulmonary arteries.

RESULTS AND DISCUSSION

In case one there was found moderately decreased ventilation of the affected lung Although there was absence of the right pulmonary artery ^{133}Xe-radiospirometry showed about 11 per cent of the total per fusion going to the affected lung, due to herniation of the normal lung into the right hemithorax. This stresses the fact that the ^{133}Xe technique as used here should not be interpreted without considering the X ray picture

In case two there was a slight decrease of the ventilation of the affected lung (12 per cent of the total ventilation) The perfusion of this lung was about 15 per cent as judged by the ^{133}Xe-technique and 12 per cent as judged by ^{131}I MAA scintigraphy There was thus good agreement between the results.

In the boy with bilateral central and peripheral stenoses of the pulmonary arteries (case three) the estimations of the regional lung function showed that the central stenoses contributed more to the pulmonary artery obstruction than did the peripheral stenoses. Thus reconstructive surgery of the central constrictions seems to be indicated.

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37 FUNNEL CHEST — A STUDY BEFORE AND TEN YEARS AFTER OPERATION

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From the 1) Childr dpt., Danderyds sjukhus Stockholm—Danderyd, 2) Med. dpt, Samariterhemmet, Uppsala, 3) Childr dpt Akademiska sjukhuset Uppsala, 4) Surg dpt Kronprinsessan Lovisas barnsjukhus Stockholm, and 5) X ray dpt, Akademiska sjukhuset, Uppsala Sweden

For many years funnel chest has encountered a fair amount of interest, from functional as well as from surgical and ethiologic points of view Very different opinions have been offered. This is understandable as far as functional and therapeutic aspects

are concerned, since a long follow-up of the patients requires not only studies of the deformity but also of the very dynamic development from child to adult. Also, very little is known about the natural history of funnel chest. Here thorough prospective studies are needed. But it must be stressed that it is almost impossible to find controls with the same physical constitution as is usual among individuals with funnel chest and who fulfil other criteria for acceptable controls.

In the study presented here we have followed a group of patients with funnel chest for 10—15 years in order to be able to evaluate the effect of surgical correction. A careful examination including heart catheterization, angiocardiography transversal tomography and ventilation capacity studies was performed before the operation. Some parents refused operation. Thus we have a control group prospectively judged in the same way as the operated cases.

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Our material shows that funnel chest has no tendency to increase with age.

Transversal tomography is the best method to evaluate the room restricting effect of the deformity An X ray in side projection gives about the same result, as the best measurement is the distance between the vertebral column and the back conture of the heart. The depth of the funnel is of little interest. Many patients have a very thin thorax. In these individuals a shallow funnel may fill out more of the thoracic cavity than a deeper funnel in a wide chest.

The examinations of heart function, lung volumes and ventilation capacity do not show any significant difference between operated and not operated patients. Operated individuals show a slight reduction of ventilatory capacity as a sign of less elasticity in the chest wall. Funnel chest patients are taller and thinner than the controls and may possibly have a somewhat lower working capacity than the controls.

The operative method has in most cases been a modification of Brown s method with a rib inserted behind the sternum.

18. OBSTRUCTIVE ANOMALIES IN THE PULMONARY VEINS OR THE LEFT ATRIUM CAUSING HEART FAILURE DURING THE FIRST YEAR

N R. LUNDSTRÖM and W MORTENSSON

From the Department f Paediatrics and Department f Radiology University Hospital, Lund, Sweden

Congenital malformations with obstruction of pulmonary venous return or blood flow through the left atrium often cause symptoms during the first year of life. The following malformations will be discussed. 1) Stenosis or atresia of one or several pulmonary veins which drain into the left atrium. 2) Stenosis of a persistent common pulmonary ...

Subdividing diaphragm in the left atrium. 4) Supravalvular stenosing ring of the left atrium associated with a parachute shaped mitral valve (Shone s syndrome) The term cor triatriatum is applied to both 2 and 3 These malformations are all rare. In Shone s syndrome there are usually other serious cardiovascular malformations but the others can exist alone. Previously they have seldom been diagnosed in vivo

The embryology of stenosis or atresia of pulmonary veins and of a persistent com mon pulmonary vein is said to be an imperfect incorporation of the common pulmonary vein into the left atrium. The stenotic and atretic changes are localized to the atrio-venous junction and are often found together When there is a persistent common pulmonary vein the vein dilatates into a »third atrium which bends into the left atrium. The diaphragm which separates these two cavities from each other consists of the walls of the vein and the left atrium, and is situated above the fossa ovalis and the auricular appendage In the other kind of cor triatriatum the left atrium is divided by an obstructing diaphragm which probably represents an abnormal growth of septum primum. The position of this diaphragm can vary in relation to the fossa ovalis and the auricular appendage. No explanation of the embryology of Shone s syndrome has been given.

These malformations all produce obstruc tion of pulmonary venous flow The pulmonary venous pressure increases and as a consequence, the pulmonary arterial pressure also increases. The symptoms usually devel op during the first year of life, being observed earlier in cases with more severe obstruction The first symptoms are usually tachypnea, intercostal retractions, and repeated respiratory tract infections. Later on, signs of right heart failure develop and then cyanosis can be seen. Murmurs, if present, are uncharacteristic.

ECG shows right ventricular hypertrophy and sometimes signs of right and left atrial enlargement. With ultrasound cardiography an abnormal echo from the diaphragm can be obtained in cases of cor triatriatum and Shone s syndrome

At roentgen examination the most important finding is the reticular pulmonary vascular marking characteristic of pulmonary venous obstruction. There is enlargement of the right heart and of the third atrium» or left atrium except in cases with stenosis or atresia of the pulmonary veins.

The pressure in the right ventricle and the pulmonary artery is increased. A pressure gradient can sometimes be found between the pulmonary artery wedge pressure and the pressure in the real left atrium in cases of bilateral stenosis of the pulmonary veins, persistent common pulmonary vein and diaphragm in the left atrium proximal to the fossa ovalis.

Angiocardiography clearly demonstrates the morphological findings in cases of cor triatriatum and Shone s syndrome. Stenosis or atresia of the pulmonary veins cannot be seen directly but there is delayed emptying of the wide and irregular involved veins.

To demonstrate the clinical manifestations and the diagnostic methods appropriate to the above mentioned malformations, four patients with pulmonary venous obstruction and right heart failure are described.

PLENARY SESSION II

TRANSPLANTATIONS AND IMMUNOSUPPRESSION IN PAEDIATRIC AGE GROUPS

CHAIRMEN GEORG RABBE WALLGREN and KAUKO KOUVOLAINEN

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39 TRANSPLANTATIONS AND IMMUNOSUPPRESSION IN PAEDIATRIC AGE GROUPS

Introduction

K. KOUVALAINEN

From the Children' Hospital, University of Turku, Turku, Finland

40 IMMUNOLOGICAL TOLERANCE

O. MÄKELÄ

From the Department of Serology and Bacteriology University of Helsinki, Helsinki, Finland

41 HISTOCOMPATIBILITY ANTIGENS AND THEIR INHERITANCE

A Review

ANJA TIILIKAINEN

From the Department of Serology and Bacteriology University of Helsinki, Helsinki, Finland

Human histocompatibility antigens have been detected at the surfaces of all kinds of nucleated cells studied so far but their amount varies in different tissues of an individual. Since most are present in high quantities on leukocytes (lymphoid series in particular), they are also called leukocyte antigens, and peripheral blood leukocytes are generally employed to determine the antigenic pattern of an individual. The genes responsible for these so-called HL-A antigens segregate in two closely linked loci of an

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Kidney The number of paediatric patients with a severe renal failure resulting in death without transplantation is quite large renal agenesis and hypoplasia, congenital nephrosis, polycystic kidneys, Wilms tumour in both kidneys, severe hydronephrosis, chronic glomerulonephritis of different etiologies. Children grafted at the age of three years or more have survived in several cases. In the younger patients the experience is too limited for evaluation of the results (1)

Liver Patients with congenital atresia of the biliary ducts very rarely survive. In this disorder liver transplantation seems to be justified despite the fact that only few patients with a transplanted liver have lived more than a couple of months. Experience, however is growing and results have improved every year

Heart and lungs. Patients with incurable congenital heart disease are very frequent. Heart transplantations have been tried even in infants. So far the results are not encouraging On very few occasions does heart transplantation seem to be the therapy of choice It should still be considered an experiment, not as a verified form of therapy in certain heart diseases. Its final value will probably be very limited. The situation is the same with the lungs.

Bone nd joints. The number of paediatric patients potentially suitable for bone and joint transplantation is large congenital anomalies, traumatic and infectious lesions, certain forms of nonspecific bone necrosis, tumours. The results of bone tissue transplantations are good and even the results of real bone and joint transplantations are encouraging So far bone and joint transplantations have rarely been made in paediatric age groups.

Skin It is a fact that a homologous skin graft rarely lives more than 10—12 days, except if an identical twin has donored the graft.

In certain congenital skin defects and plastic operations, trials should be made using skin grafts from donors who are compatible with the recipient in respect to the major histocompatibility antigens.

Bone marrow and lymphatic tissues. The need for renewal of the blood forming and/or antibody forming cells is a well-known fact in several haematological diseases and congenital immunological deficiency states. Bone marrow transplantations have been tried with a certain success in aplastic anemias of different etiologies. In the immunological deficiency states, the results had been discouraging until last year when de Koning et al. (2) succeeded in rebuilding the immunological capacity of an infant with the Swiss type of agammaglobulinemia. They transplanted special bone marrow cells and a fetal thymus. The donors' histocompatibility antigens were very similar or nearly identical with those of the recipient. After the grafting the patient has developed perfectly normally It seems justified to predict that with careful selection of a compatible donor with special purposeful selection of the cells to be transplanted and with strict sterility during postoperative care, many patients now judged as hopeless will even be permanently cured. Of all transplantations, bone marrow and lymphatic cell grafting seem most promising for the future of paediatrics.

Endocrine glands. Endocrine glands have been transplanted to experimental animals with a certain success. This might seem promising for paediatric endocrinology Substitution therapy with synthetized or extracted natural hormones has, however succeeded so well that the writer sees no need for treatment of these disorders by transplantation.

The overgrowth of the population of the world and birth control are central problems also in medicine. One may ask whether there is any sense in transplanta

autosomal pair of chromosomes. Nine codominant, mutually exclusive HL-A genes are known to alternate at the first sublocus and thirteen at the second sublocus. Accordingly 9 × 13 combinations of these alleles gives rise to 117 different chromosomes, which indicates that at least 6903 phenotypes should occur in the population.

The correlation of any given HL-A gene or phenotype with a disease will be hard to demonstrate, due to the high number of variable genes. There is reason to believe, however that histocompatibility antigens have great biological significance They are often called transplantation antigens, because graft survival is more closely correlated with their compatibility in donor and recipient than with any other known genetic system in man. In analogy with mouse leukaemia it has been suggested that human leukaemia might prevail in people with certain leukocyte antigens. Pregnant women frequently produce antibodies to the foetal HL-A antigens inherited from the father· these antibodies however seem to be mainly harmless to the foetus. Some correlation with mild obstetric or paediatric irregularities was suggested in one series of delivery histories analyzed by our team. In our opinion, the production of anti HL-A antibodies is physiologically desirable. Complications are predictable if the antigenic stimulus is too small to cause an immunological response, or if the pregnant woman is unable to produce enough antibodies (low fertility chorionepithelioma, nephrogestosis) A few studies suggest that the foetus may become tolerant to the maternal HL-A antigens. Possible correlations between organ transplantation and such tolerance deserve to be investigated. It is now possible to selectively eliminate one cell population from a mixture of cells carrying different HL-A antigens. Sperm being one such mixture of haploid cells, we may imagine the day when histocompatibility antigens will play a part in artificial insemination.

42. PAEDIATRIC ASPECTS OF TRANSPLANTATIONS

K. KOUVALAINEN

From the Children's Hospital University of Turku, Turku, Finland

During the last few years organ and tissue transplantations have achieved great success. We can without hesitation consider transplantations a significant part of modern medicine. The great success and publicity may on the other hand, entice physicians to heroic adventures and experiments in the field of transplantations which are perhaps not always in accordance with practical medical needs and the very sense of medicine Transplantations are gaining ground more and more in the field of paediatrics, too In this paper an attempt has been made to find out the need of transplantations in the paediatric age groups and to discuss the special and ethical problems.

At the present stage of knowledge we can not yet set the final long term prognosis for children with transplanted organs or tissues. After several years of observation, the prognosis seems, however to be good in certain forms of transplantations. In the present

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The mechanism by which the immunosuppressive drugs increase tolerance of the transplant is manifold and not precisely known. They inhibit different phases of the immune reaction and in addition there may be also a simple anti-inflammatory effect.

The effects of these drugs on immune reactions may be difficult to regulate and they can sometimes have an opposite harmful effect.

All immunosuppressive drugs are toxic. Corticosteroids have many wellknown side effects but in paediatrics we must also recall their inhibitory effect on growth.

The most common complication is bone marrow depression with macrocytic anaemia, leukopenia and thrombocytopenia. Hematological complications caused by 6-MP and cyclophosphamide are usually reversible and disappear when the dose is reduced or stopped. Infection is not so common as one might suspect. Viral infections are common. Azathioprine and 6-MP have caused toxic hepatitis.

There is a lack of well controlled comparative investigations of the immunosuppressive drugs made with the double blind method. We need these investigations more than new drugs to be tested.

45 IMUREL® THERAPY IN AUTOIMMUNE DISEASE STATES

B. BJÖRKSTÉN and K. M. LUNDMARK

From the Department of Paediatrics, University Hospital, Umeå, Sweden

We have conducted a clinical trial of immunosuppressive therapy with azathioprin (Imurel®). The indication was an established diagnosis of autoimmune disease, severe in nature, in which other treatment, primarily corticosteroids, had either failed or been accompanied by serious side-effects. The initial dose was 2.5—3.0 mg/kg in 1 (-3) dose(s); this was continued for at least one month to permit evaluation of the effect. If there was no improvement, the dose was increased to 3.5—4.0 mg/kg, occasionally to 5.0 mg/kg. If there was improvement, the dose was maintained for 6 months and then decreased by 1—1.5 mg/kg at 6 months' intervals. Control testing consisted of a complete determination of the blood status once a week fo 4—6 weeks initially and after each increase in dosage, thereafter every 4 weeks. After reduction of a well tolerated dose the blood status was controlled every 6—8 weeks. If the total number of WBC fell to 3 000/mm³ or the granulocytes to 1.500/mm³ the blood was checked frequently and the dose was sometimes decreased. If the values were under 2.000 or 1 000 respectively Imurel® was omitted for at least two weeks, and resumed, if necessary in a reduced dose. Liver and kidney function and serum immunoglobulins were checked initially every 4—6 months.

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27 children, aged 3 months to 16 years, have been treated for from 1 to 28 months (a total 1 318 months). Their diagnoses and the results

tions compared with the huge socio-medical problems mentioned above One cannot, however accept the thought that defective infants and children should not be treated because there are too many people in the world. Such thinking would deny the whole basis of medicine As soon as a new human being is born, we shall offer him the best medical care. In this care transplantations offer one real though limited possibility

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43 SURGICAL ASPECTS OF TRANSPLANTATIONS IN CHILDREN

B. LINDSTRÖM

From the University Central Hospital, Helsinki, Finland

44 ASPECTS OF IMMUNOSUPPRESSIVE DRUGS

A Review of Literature

P RANTANEN

From the Children s Hospital University of Turku, Turku, Finland

At present there are more than 100 immunosuppressive agents. They are divided into five groups by chemical structure and the mechanism of effect

1 Alkylating agents
2. Purine analogues
3 Pyrimidine analogues
4 Folic acid antagonists
5 Corticosteroids

Schwartz and Dameshek were the first to demonstrate the successful effect of 6-mercaptopurine in skin transplantation in 1960 Azathioprine, which is chemically nearly related to 6-MP has the same effect and many investigators think it easier to use and less toxic. Some investigators, however h not been able to demonstrate this differe and they use 6-MP

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Table 1 *Patients treated with Imurel® (May 1970)*

Diagnosis	Number	Effect of treatment			
		Recovered	Improved	Unimproved	Unable to evaluate
Lipoid nephrosis	5	4	—	1	—
Nephrosis status post Henoch Schönlein	2	1	—	1	—
Congenital nephrosis	1	—	—	1	—
Chronic glomerulonephritis	1	—	—	1	—
Rheumatoid arthritis	3	—	1	1	1
S.L.E.	2	—	—	—	2
Dermatomyositis	2	—	2	—	—
Scleroderma	1	—	—	—	1
Recurrent parotitis	1	—	1	—	—
Recurrent uveitis	1	—	—	1	—
Chronic active hepatitis	1	—	—	—	1
Ulcerative colitis	1	—	—	1	—
Pulmonary hemosiderosis	2	—	1	—	1
I.T.P	1	1	—	—	—
Myasthenia gravis	1	—	1	—	—
Polyradiculoneuritis	1	1	—	—	—
Sclerosis diss.	1	—	—	—	1
	27	7	6	7	7

of treatment are given in Table 1 Of the 20 patients in whom evaluation was possible 7 have apparently recovered, 6 have improved, and 7 are unimproved. None has deteriorated. Improvement has been striking in several cases and the beneficial effects of Imurel® therapy have been impressive We have taken into account the fact that corticosteroids have a *synergistic effect*. 7 patients received steroid therapy for too short a time for purposes of evaluation. One patient with minimal changes on kidney biopsy who was unimproved after 4 months of steroid Imurel® therapy improved dramatically following a life-threatening sepsis *that was treated intensively and after which* administration of cyclophosphamide (Sendoxan®) was instituted. One case of scleroderma of a very severe nature died of heart failure 1 month after the start of Imurel® therapy In a patient with congenital nephrosis, 4 months of Imurel® therapy had, as expected, no effect.

Side effects In several cases there was leucopenia to the level of 3 000 WBC/mm^3 In one patient with rheumatoid arthritis a severe hypoplastic bone marrow reaction appeared after 11 months of treatment with 2.5—3 0 mg/kg this was promptly reversed when Imurel® was omitted. Otherwise, Imurel® was tolerated without apparent side-effects There has been no evidence of increased susceptibility to infection or of abnormal immune response nor *has malig*nancy arisen in any patient.

CONCLUSION

The results of the clinical trial with Imurel® are encouraging

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Key words Immunosuppressive therapy auto-immune diseases in children

46 EXPERIENCES WITH SEVEN RENAL HOMOTRANSPLANTATIONS IN CHILDREN

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During the period 1967—1969 seven renal homotransplantations were performed in children under 16 years. The patients are a part of a larger group of transplantation material published elsewhere (B. Kuhlbäck et al., Scand. J. Urol. Nephrol. 1970, in print). The youngest patient was 9 years old and the mean age was 12½ years. The diagnosis was chronic glomerulonephritis in four cases, interstitial nephritis, nephrocalcinosis and hereditary nephropathy in the others. All patients were uraemic and six of the seven were dialyzed 2—17 times before the transplantation. All had hypertension, retinopathy and anaemia. Somatic development was retarded.

The mother was a donor in four cases and the father in three. Two patients had B-match, two C-match, two D-match and one patient E-match in histocompatibility (symbols according to Kissmeyer—Nielsen et al., Transpl. Proc. 1,357—361, 1969) (Table 1).

Bilateral nephrectomy was performed in connection with transplantation in six patients, unilateral nephrectomy in one patient, whose other kidney was removed one month later. The duration of cold ischaemia was 50—55 minutes in most cases. Urine production began immediately and serum creatinine normalized (under 1.0 mg/100 ml) during a few hours. Urine volume reached its maximum (5000—9000 ml/day) during the next 2—4 days and was normal (1500—2000 ml/day) after 10—14 days. Approximately after one week creatinine clearance was 70—120 ml/min and phenolsulphonphtalein excretion 60—90 %/2 h. Immunosuppression therapy was started on the day preceding the transplantation with prednisone (2,0—2,5 mg/kg/day) and azathioprine (2,0—3,5 mg/kg/day). After the first two weeks the doses of prednisone were reduced gradually to about 0,1—0,3 mg/kg/day and that of azathioprine to 1,0—2,0 mg/kg/day.

The time of the follow up is now 1 yr. 2 mo. — 3 yrs. 6 mo. (in four patients over 2 yrs.). One patient died one month after the transplantation in gastrointestinal bleedings with

Table 1

Case no	Sex	Age (yrs)	Kidney disease and its duration (yrs)	Donor (age, yrs)	Histocompatibility
1	F	11	Chronic glomerulonephritis (4 years)	Mother (33)	D-match
2	M	15	Nephrocalcinosis (> 10) (Vitam. D-overdos.)	Mother (35)	B-match
3	F	11	Interstitial nephritis (2—3)	Mother (43)	C-match
4	M	13	Chronic glomerulonephritis (2)	Father (47)	E-match
5	F	15	Chronic glomerulonephritis, Hypopl. ren. dx. (3)	Father (43)	C-match
6	F	14	Chronic glomerulonephritis, Hypopl. ren. dx. (2)	Father (50)	B-match
7	M	9	Familiar nephropathy (Fanconi?) (6)	Mother (42)	D-match

Table 1 *Patients treated with Imurel® (May 1970)*

Diagnosis	Number	Effect of treatment			
		Recovered	Improved	Unimproved	Unable to evaluate
Lipoid nephrosis	5	4	—	1	—
Nephrosis status post Henoch Schönlein	2	1	—	1	—
Congenital nephrosis	1	—	—	1	—
Chronic glomerulonephritis	1	—	—	1	—
Rheumatoid arthritis	3	—	1	1	1
S.L.E.	2	—	—	—	2
Dermatomyositis	2	—	2	—	—
Scleroderma	1	—	—	—	1
Recurrent parotitis	1	—	1	—	—
Recurrent uveitis	1	—	—	1	—
Chronic active hepatitis	1	—	—	—	1
Ulcerative colitis	1	—	—	1	—
Pulmonary hemosiderosis	2	—	1	—	1
I T.P	1	1	—	—	—
Myasthenia gravis	1	—	1	—	—
Polyradiculoneuritis	1	1	—	—	—
Sclerosis diss.	1	—	—	—	1
	27	7	6	7	7

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47 THE CONGENITAL NEPHROTIC SYNDROME — AN INDICATION FOR KIDNEY TRANSPLANTATION?

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The congenital nephrotic syndrome is a hereditary fatal disease unresponsive to any conservative treatment. After bilateral nephrectomy followed by peritoneal or haemodialysis treatment a distinct improvement in the condition of these patients may be achieved. The technical fulfilment of a kidney transplantation to these patients in their early infancy has proved to be difficult. The abnormal vascular conditions cause new problems the transplantant may not be placed in the way generally accepted in most transplantation centres. The neonatal cadaveric donors form a quite special problem in testing immunological compatibility before transplantation. These problems will be discussed preliminarily in the light of a few case reports.

Table 2

Case no	Follow up	Blood press	Serum creat. mg/100 ml	Creat. clear ml/min	PSP excr %/2 h	*Complications*
1	3 yrs. 6 mo.	120/80	1,2	60	67	— reject. after 6 weeks — strict.uret. after 1½ yrs — urinary inf. after 2 yrs — now proteinuria
2	1 mo					death after 1 month in gastrointest.bleedings
3	3 yrs. 3 mo.	150/120 (medic.)	1 7	48	46	— reject.after 6 mo. — nephrotic syndr — hypertension
4	2 yrs. 2 mo.	135/90	1,8	52	42	— rejection after 6 weeks
5	1 yr 11 mo	110/70	0,9	119	65	— reject. after 4 weeks — urinary inf. after 2 yrs.
6	1 yr 6 mo.	140/110	2,1	40	35	— reject. after 1 week — reject. after 6 weeks — reject. after 6 months — chr reject. after 1 yr. — hypertension
7	1 yr 3 mo	130/90	1 6	42	36	— reject. after 2 weeks — reject. after 5 months — reject. after 8 months — encephalitis after 8 months

peritonitis but his kidney function was quite normal Four patients have had one rejection usually 3—6 weeks after transplantation. More rejections have occurred only in two children Rejections in children usually seem much stronger and more acute than in adult patients, who mostly have a picture of slow or chronic rejection. During rejection all patients had high fever with hypertension, raised serum creatinine oliguria, pathological isotope nephrography and changes typical of fine needle aspiration biopsy The therapy in the rejections was, besides higher doses of prednisone (3—5 mg/kg/day) and azathioprine (2,5—3 0 mg/kg) local irradiation of the graft (the total dose being 600—1000 r) and actinomycin C 200 μg every other day until the rejection was over

One patient got a nephrotic syndrome seven months after transplantation, but is now in good condition. Other complications were urinary infection in two patients, strictura ureteris in one and encephalitis in one patient. Four patients have now normal blood pressure two others have moderate hypertension. Creatinine clearance is now over 50 ml/min in three patients (52—119 ml/min) and between 40—50 ml/min in the others. Phenolsulphonphtalein excretion is over 60 %/2 h in two children and between 35—50 %/2 h in the others. Retinal changes have almost totally regressed. Little or almost no osteoporosis has been observed. The skeletal age is approximately ½—1½ yrs lower and only in one patient 2 yrs higher than the calendar age Height growth has been minimal (Table 2)

All living patients (6/7 attend school, move actively and are no longer bound to the dialysis centres. All of them still have immunosuppression therapy (prednisone 0 1—0,3 mg/kg/day and azathioprine 1 0—2 0 mg/kg/day) Most routine controls are carried out at local hospitals, but thorough check ins take place every six months in the transplantation centre

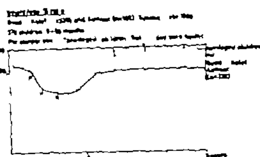


Fig. 1 Weight/age expressed as % of median of Harvard standard (2) in 372 children, examined in February 1969 in Ouad-el-Khatef and Armour Tunisa. For comparison, the weight/age of 36 privileged children, at a day care centre in Kebbia is plotted.

Table 1 *Prevalence (%) of some clinical signs in 372 children, 0—60 months, examined in February 1969 in Ouad-el Khatef and Armour Tunisa.*

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live born infants at the MCH in 1968 was 3.379 g

During the period 6 months to about 2 / years the physical development was poor coinciding with the period of weaning. This is most obvious in terms of weight development (Fig. 1) but is also noticeable in other anthropometric measurements and in the rate of clinical signs of protein-calorie malnutrition. In the age group 12—23 months no less than 21.6 % had wasted flabby muscles. A total of 2.7 % had a severe marasmus or marasmic kwashiorkor requiring hospital treatment.

Table 1 shows a few other positive findings in the base-line survey. The rate of *rickets* was high, amounting to no less than 39 % during the second half year of life. *Angular stomatitis* suggestive of ariboflavinosis was diagnosed in 12.9 % in the total material. 18.2 % of the children over 6 months had *anemia* (according to WHO defined as Hb less than 11 g / (3)). The majority had a mild anemia, with Hb 9—11 g %.

A low MCHC (below mean minus 2 S.D. in 85 % of the anemia cases indicated iron deficiency. Table 1 also indicates that a considerable number of children were suffering from skin infections, scabies and worm infestations.

Some important *seasonal variations* seem to occur. The base-line examination took place just at the end of the cold winter (November February). In October after the long hot summer a follow-up examination was made in the village of Armour. The rate of rickets had now decreased from a total of 12.9 to 1.4 %. In the last follow-up examination in February 1970 the rate was up again, but only to 6.8 %, which can probably be ascribed to the unusually mild and sunny winter. After the summer season, on the other hand, the percentage of children with signs of PCM was higher than in February as was the rate of skin infections and similar ailments. The increased rate of PCM is certainly an effect of the higher frequency of diarrhoeal disease during the summer months. It should be borne in mind that PCM is most often the result of the combined effect of dietary insufficiency and infections. Also the rate of skin affections was 3—4 times higher in October.

If the situation in February 1969 and 1970 is compared, no major changes (except for rickets — see above) had taken place. The MCH activity in the village of Ouad-el Khatef had only been in operation for 9 months and it would be too optimistic to expect any major improvements in such a short time. However it appeared that the instructions about home made weaning foods had been understood and remembered by the great majority and some 40 % were preparing such dishes regularly as against about 4 % half a year earlier.

SESSION A II

METABOLISM, INFECTIONS

CHAIRMEN PETER KARLBERG and MARTIN SEIP

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46 NUTRITION STUDIES IN TUNISIA

M. BÖRJESSON and Y. HOFVANDER

From the PMI Kelibo, Tunisia and Department of Paediatrics University Hospital, Uppsala, Sweden

Since 1963 Sweden has been involved in a bilateral assistance programme at the Cap Bon peninsula in North-eastern Tunisia. It comprises a fishing school and a maternal and child health centre started in 1965 and located adjacent to a small county hospital.

In the curative and preventive work at the child health centre cases of severe protein calorie malnutrition (PCM) are frequently diagnosed, particularly after the hot summer when the rate of gastro-intestinal infections is also high.

The purpose of this paper is to report on a more detailed survey of the nutritional situation in children below 5 years in two typical villages at the Cap Bon peninsula. The two villages, Ouad-el Khatef and Azmour have about 1 000 inhabitants each, all houses are numbered and everybody is registered at the office of the village chief. With few exceptions the birthdate and the ages of the children were known. 80—90 % of the heads of households were daily workers at the cooperative farms, only 8—9 % of them had attended school for more than 1 year and 1.5—4.6 % of their wives in the respective villages. The infant mortality rate as revealed through interviews was 241 in Ouad-el Khatef and 185 in Azmour and the total mortality rate 0—5 years per 1 000 live born was 357 and 323 promilles respectively.

A base-line examination was made in both villages in February 1969 in 372 children 0—60 months, comprising anthropometric, clinical and laboratory data.

This represents 100 % of the children in this age group. A dietary survey was made on a subsample. Follow up surveys have been made after 1/2 year (in Azmour) and 1 year partly to study seasonal variations and partly to evaluate the effect of a nutrition education programme in the village of Ouad-el Khatef.

RESULTS

As there were only minor differences between the villages, they will be presented together.

The physical development during the first few years was similar to that reported from many developing countries. The birth weight and the increase in weight and length during the first few months was similar to Western standards. The average birth weight of 657

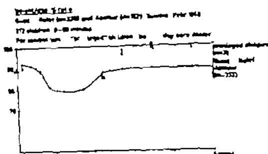


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SUMMARY

A base-line nutrition survey was made in two Tunisian villages at the Cap Bon penin sula in February 1969 Follow up examina tions were made in October 1969 and in February 1970

It is concluded that the physical develop-ment is poor during the »transitional period from about 6 months to 2½ years and the majority of children pass through a stage of mild moderate PCM as indicated by clinical and/or anthropometric signs. Other deficiency diseases were not uncommon, e.g rickets, which however showed marked seasonal variations.

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49 ASPARTYLGLUCOSAMINURIA, CLINICAL ASPECTS

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Aspartylglucosaminuria is an inborn error of metabolism, characterized by an accumula tion of 2 acetamido-1-(β' L-aspartamido)-1,2 dideoxy β-D-glucose (AADG) in urine (2) This accumulation is thought to result from a disorder in the catabolism of glycoproteins, possibly based on a lysosomal enzyme defect. Twenty patients have now been found in Finland, 10 males and 10 females Eight of the patients were children. The preliminary data were as follows (1)

The patients were from different parts of the country The age distribution was 5—37 years, with four male-female pairs of sib-lings In one case the parents were first cousins There were no remarkable pre- or perinatal disorders The patients had recur rent infections, often already in early life They had coarse features, slightly resembling those seen in gargoylism acne-like dermatitis or exanthema in some hernias and skeletal abnormalities. Some had an enlarged liver The patients seemed to be mentally retarded. Some had psychotic eretic episodes.

A more detailed study including neuro-physiological, psychological, biochemical, his-tochemical and X ray investigations, was started.

The preliminary anamnestic and clinical findings were confirmed All patients had typical features with a low bridge of other wise broad nose, big mouth, thick lips, a rather big face, and epicanthus in some These features were not so prominent in children as in adults. Some of the patients were hypotonic, one had a mild spastic dip-legia. They had clumsy motor function and a peculiar forward leaning way of running The first sign of retardation in many cases was delayed development of speech. The age of appearance of these signs varied from some months to 7 years. In some cases the history was suggestive of a progressive dementia. The children were less severely retarded, com pared with the adults.

The urinary amino acid electrophoreto-grams of clinically normal family members have shown no abnormalities yet. There may

be a trend to an increased frequency of psychoses among the relatives.

The patients have shown no clear abnormalities in the levels of serum calcium, potassium and alcalic phosphatase, in the liver function tests, creatinine levels and in routine urine and CSF investigations. All excreted AADG in urine, as examined with high voltage electrophoresis and two-dimensional paper chromatography. Heating the paper at 100 C changes the originally brown colour of AADG into blue-green and confirms the diagnosis. All patients had vacuolised lymphocytes and monocytes in blood and also in some examined bone marrow specimens, varying from less than one to 50 per cent. Chromosome studies have shown no abnormalities. EEG-recordings have revealed no remarkable and no specific changes. Mild diffuse abnormalities have been found in some.

X-ray investigations showed diffuse skeletal changes including a generally thin cortical layer of bones, thick skull bones, underdeveloped frontal sinuses and spinal deformities. There may be an increased frequency of spina bifidas with varying spinal distribution. One of the patients had signs of pathological fractures. PEG and carotic angiography performed in one case earlier showed very mild, diffuse atrophy of brain and slow cerebral circulation.

Because no comprehensive control material has been screened, the prevalence of aspartyl glucosaminuria among normal population is unknown. The high frequency of the disease in Finland may be due to the fact that the genetics of several hereditary metabolic diseases is different in this country as compared with many other European countries. This is evident for instance in the case of phenylketonuria. On the other hand, the spot of AADG in the urinary amino acid chromatogram, without the heating procedure, may be very weak and may be misinterpreted as an artefact or neglected.

Grants: Kehitysvammaliitto r.y. the Finnish Medical Foundation.

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Key word. Aspartylglucosaminuria

50 MAPLE SYRUP URINE DISEASE VARIANT — AMINO ACID PATTERN AND PROBLEMS OF TREATMENT DURING ACUTE ATTACKS

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More than 50 cases of the MSUD in the newborn period have been recorded since the first report by Menkes et al. in 1954. (7) The introduction of dietary treatment with low amounts of the three branched chain amino acids has given these children the possibility of survival, even with normal cerebral function. Diet however is not always able to

Table 1 *Serum amino acids one day after morbilli vaccination fever (episode no 1) during (a) and one day after (b) fever due to upper respiratory infections (episodes no 2 3 and 4). All results are expressed in μmol per liter serum.*

Episode	1	2 (a)	2 (b)	3 (a)	3 (b)	4 (a)	4 (b)	Normal values for this child
Valine	1935	91 —	253	153 —	131	360 —	1455	141
Alloisoleucine	160	0 —	0	0 —	0	0 —	94	0
Isoleucine	1022	31 —	90	46 —	38	139 —	786	42
Leucine	2406	91 —	245	145 —	102	374 —	1965	111
Phenylalanine	135	54 —	103	52 —	45	100 —	64	70
Treatment	fluids paren terally	small amounts of sulfa		penicillin B-vitamins C vitamin		pyridoxin		

prevent death in acute exacerbations of the metabolic process during infections

The late-manifesting variant of MSUD was described by Morris et al. in 1961 Since then 7 cases have been reported (2 3) These chil dren develop normally but following certain intercurrent diseases — such as acute infec tions — they may turn acidotic, comatose with convulsions, present the smell of maple syrup clinically resemble encephalitis and possibly succumb in an acute attack. This variant presents, in an acute attack, excess of leucine isoleucine valine and their cor responding ketoacids in serum and urine. A defect in the decarboxylation mechanism of the white blood cells and the fibroblasts has been shown to be present in the classic MSUD and less pronounced in the variant type (1)

A new case of MSUD-variant was diagnosed in Norway in 1969 A two-year-old girl presented coma acidosis and convulsions 8 days following measles vaccination with febrile reaction.

This episode and subsequently 3 other acute attacks following respiratory infections were registered by quantitative amino acid deter mination in serum, see Table 1 A particular elevation of phenylalanine was noted. This is, as far as we know not previously reported in MSUD We tried to influence the disease with decarboxylase co-factors.

As can be seen from Table 1 the branched-chain amino acids were normal after the fever in episode no 3 when penicillin and vitamin B and C were given In contrast the same amino acids were elevated in episodes no 1,2 and 4 which were treated with parenteral fluid, small amounts of sulfa and vitamin B_6 respectively Urinary amino acids showed the same pattern.

The elevation of the branched chain amino acids in the variant type usually develop in relation to acute infections with fever In our patient the metabolic derangement and clinical signs were present the day after high fever

In order to counteract this metabolic dysfunction it seems to be important to treat the infections early reduce the fever and supply the patient with sufficient water soluble vitamins. Our experience has shown that oral feeding is difficult due to vomiting. Therefore proper intravenous feeding with low content of branched-chain amino acids together with carbohydrate and fat in order to reduce the catabolic process in the body may be necessary if the infection and the fever are not treated early enough.

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Key words. Maple Syrup Urine Disease Variant amino acid pattern, decarboxylase co-factors, phenylalanine elevation.

51 PITUITARY DWARFISM. TREATMENT WITH HUMAN GROWTH HORMONE

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Human growth hormone (HGH) commercially prepared by AB Kabi according to Roos et al. (1) was used in the treatment of sixteen patients with short stature due to lack of pituitary growth hormone. The aim of this study was to establish the minimal dosage of this HGH preparation, which initiated and maintained a satisfactory growth rate. Fur thermore we wanted to compare its effectiveness with HGH from two other sources, Roos and Raben.

Sixteen patients ranging in age from 8—18 years were treated for 9—24 months with HGH Kabi. Eleven of the patients were previously treated with other HGH preparations for periods ranging from 1—5 years. The diag nosis of growth hormone deficiency was established by the following criteria. 1) Short stature and slow growth rate. 2) Retarded skeletal and dental development. 3) Absent response of plasma growth hormone to insulin induced hypoglycemia bef re and during treatment with l-thyroxine Deficiencies of ACTH and TSH were established by Metyrapone test, PBI and radioiodine uptake before and after TSH. None of the patients showed any signs of puberty Three of the patients had an isolated growth hormone deficiency five had in addition a deficiency of TSH and nine deficiencies of TSH and ACTH.

One mg of the Kabi's preparation and of the original Roos preparation was equally potent as determined by radioimmunoassay and corresponded approximately to 2 U of the first international reference preparation of human growth hormone for immunoassay (National Institute for Medical Research, London). Raben s HGH contained approximately 1.0 U/mg The initial dosage of Kabi s HGH was as a rule 4 mg per week divided into two doses. If there was insufficient growth after 6—12 months of treatment, the dose was increased to 5—6 mg per week in two or three doses.

Five patients recieved Kabi s HGH as the first preparation. Four of these patients showed an increased growth rate, 5 7—8.9 cm/year as compared to the pretreatment growth of 1.0—3 3 cm/year Their growth rates corresponded to their physiological ages as evaluated by bone age and increment data of Tanner et al. (2), but there was no catch up growth. One patient did not respond to a dose of 4 mg per week, but started to grow on the increased dose. When the dosage was examined on a mg/kg body weight (BW) basis,

this patient had only received 0 105 mg/kg BW per week. The other four patients had been treated with a weekly dose of 0 125—0.260 mg/kg BW The four patients initially treated with Roos s original HGH preparation showed an increased growth rate, 5 6—18 0 cm/year The two patients that showed catch up growth of 8 7 and 18 0 cm/year received a weekly dose of 0.288—0 515 mg/kg BW whereas the other two received 0 156—0.211 mg/kg BW Three patients were originally treated with Raben s HGH Two of these grew 3.3 and 4 6 cm/year on a weekly dosage of 0 350 mg/kg BW The third patient grew 11.3 cm/year on 0.560 mg/kg BW

In nine of the eleven patients in which Kabi s HGH was the second or third preparation used on weekly doses of 0 150—0.275 mg/kg BW the growth rate corresponded to their physiological age. Two patients without a normalized growth rate on 0 150 mg/kg BW per week, started to grow when the dose was increased.

Cortisone in a low substitution dose did not change the growth rate in the patients requiring corticosteroids No antibodies against growth hormone were detected in any patients receiving Kabi s HGH One patient showed high titers of HGH antibodies and growth failure after being treated with Raben s HGH. The titer decreased and the growth rate increased when treatment was changed into Kabi s HGH.

It would seem from our experience that treatment with HGH should be undertaken with consideration of the dosage per kg BW In our study most cases received too low a dosage to obtain optimal catch up growth. Our preliminary data suggest that with a weekly dose of 0.20 mg Kabis HGH/kg BW it is possible to obtain a normal growth rate but it will be necessary to use a dose of 0.30 mg/kg BW to obtain an optimal catch up growth. We cannot compare our results with those of other authors (2) showing catch up growth in pituitary dwarfs during treatment with HGH as these authors were only reporting the dosage in mg per week independent of body weight.

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Key words Human Growth Hormone Therapy Pituitary Dwarfism, Growth rate

52 MULIBREY NANISM DWARFISM WITH MUSCLE, LIVER, BRAIN AND EYE INVOLVEMENT

J PERHEENTUPA, S AUTIO S LEISTI and C. RAITTA

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We report on a syndrome of proportionate prenatal-onset dwarfism, previously unknown to us, which we saw in two boys and two girls from five to 16 years of age They were strikingly similar in appearance and in their abnormalities. The characteristics were triangular face with bulging forehead, low nasal bridge and mildly hydrocephalic appearance, scaphocephaly thin and hypotonic extremities, prominent veins on the forehead and neck presumably due to cardiac myopathy hepatomegaly variable ocular changes,

normal karyotype, peculiar high-pitched voice, and slightly subnormal intelligence.

No other similar cases were known in the four families, and other family members were of normal stature. As yet no consanguinity could be found between any of the eight parents but several of the ancestors were from the same area in southeastern Finland. The pregnancies were uneventful. Three were born 1 ½—3 weeks before term with weights and lengths at or below the 10th percentile for gestational age, one had normal weight. The immediate condition was good, but two had to be hospitalized soon because of poo nursing Bilateral fracture of radius was found in one at three weeks of age. Hepatomegaly was noted in one already in the neonatal period. All had severe respiratory infections recurring from early life. Growth was consistently severely retarded from the beginning with height between 4.5 and 6 S.D below the median for age. The ratio sitting-height/height was normal for height but the span was on the long side of the median for height. The ponderal growth was m re retarded, with weight more than 2 S.D below the median for height in three. The skeletal maturation was not consistently delayed. The motor development was mildly to severely retarded in the first years.

All had general muscle hypotonia but no distinct localizing neurological signs. EEG was normal or showed mild diffuse abnormality with increased theta and delta-activity Pneumoencephalography revealed slightly or moderately dilated ventricles and basal cisternas. One had an extra cavity presumably a dilatation of the aqueduct. A primitive trigeminal artery was found in one by carotid angiography CSF was normal including protein pattern.

Abnormal dispersion of retinal pigment was found in three. One had a lattice-like corneal dystrophy and another similar but milder changes. Both had nuclear lenticular opacities. The two others had monocular converging squint with amblyopia. ERG was normal or subnormal and incompatible with retinal heredodystrophy

EMG nerve conduction velocity muscle histology and ATP and creatine phosphate concentration, and serum LDH, CPK and aldolase activities were normal.

The sella turcica was long-shaped with low anterior ridge, slightly like that in hydrocephalus. The base was short compared with the length of the skull. The long bones were thin with normal cortical thickness. The a-p diameter of lumbar vertebrae was short relative to their height.

Two had large cutaneous vascular naevi.

The liver was markedly enlarged. Only one had sure splenomegaly Histological and histochemical examination of needle specimens of liver revealed no distinct signs of chronic congestion, inflammation, or cellular deposits. Clear fibrotic changes were seen in one only Glucosaemia, serum protein pattern and GOT activity galactose and bromsulphonphtalein elimination, glycogen mobilization by glucagon, and plasma and urine amino acid patterns were normal. Growth hormone release on hypoglycaemia, serum PBI, and hypothalamo-pituitary-adreno-cortical responsiveness were normal. Urinalysis, SUN and urogram were normal. Tests of intestinal absorption gave normal results.

All had increased dyspnoea on exercise, raised venous pressure and early clubbing of the fingers. The heart was clearly enlarged in one only who was shown to have open foramen ovale by catheterization. The cardiac findings including ECG suggest primary abnormality of the heart muscle.

this patient had only received 0 105 mg/kg BW per week. The other four patients had been treated with a weekly dose of 0 125—0.260 mg/kg BW The four patients initially treated with Roos s original HGH preparation showed an increased growth rate 5 6—18 0 cm/year The two patients that showed catch up growth of 8 7 and 18 0 cm/year received a weekly dose of 0.288—0.515 mg/kg BW whereas the other two received 0 156—0.211 mg/kg BW Three patients were originally treated with Raben s HGH. Two of these grew 3 3 and 4 6 cm/year on a weekly dosage of 0.350 mg/kg BW The third patient grew 11 3 cm/year on 0.560 mg/kg BW

In nine of the eleven patients, in which Kabi s HGH was the second or third preparation used, on weekly doses of 0 150—0.275 mg/kg BW the *growth rate corresponded to* their physiological age Two patients without a normalized growth rate on 0 150 mg/kg BW per week, started to grow when the dose was increased.

Cortisone in a low substitution dose did not change the growth rate in the patients requiring corticosteroids. No antibodies against growth hormone were detected in any patients receiving Kabi s HGH. One patient showed high titers of HGH antibodies and growth failure after being treated with Raben s HGH. The titer decreased and the growth rate increased when treatment was changed into Kabi s HGH.

It would seem from our experience that treatment with HGH should be undertaken with consideration of the dosage per kg BW In our study most cases received too low a dosage to obtain optimal catch up growth Our preliminary data suggest that with a weekly dose of 0.20 mg Kabis HGH/kg BW it is possible to obtain a normal growth rate, but it will be necessary to use a dose of 0.30 mg/kg BW to obtain an optimal catch up growth We cannot compare our results with those of other authors (2) showing catch up growth in pituitary dwarfs during treatment with HGH as these authors were only reporting the dosage in mg per week independent of body weight.

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52. MULIBREY NANISM DWARFISM WITH MUSCLE, LIVER, BRAIN AND EYE INVOLVEMENT

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This study reports the results of URI GLOX® as a screening method for bacteriuria among 2016 children, aged 4—19 years.

METHODS

The study is a part of a general health control, partly of 4-year-old children (448 girls and 490 boys) and partly of schoolgirls (1063 girls).

The urine samples were collected at home under standardized conditions. The midstream morning specimen was voided without prior periurethral cleansing directly into the steril testube after 4—8 hours retention of urine in the bladder

N eating or drinking was allowed during the night. The sample was chilled with ice cubes in plastic bag and delivered during the day to the laboratory for bacteriological culture and testing with URIGLOX®

All cultures showing growth of any organism considered t be pathogenic for the urinary tract as well as any pathological reaction of the test paper led to the collection of new samples. Generally repeated samples were requested until two consecutive samples were normal

RESULTS

Instructions

The effectiveness of the instructions was recorded in detail for the first 1459 children examined. For the remaining 554 children, the retention time only was noted. Almost 90 per cent of the children followed the instructions in all respects (Table 1). In none of the children not following the instructions was significant bacteriuria demonstrable in additional samples.

Bacteriology

The results of the bacteriological cultures of the first samples from the 1847 children

Table 1 *Effectiveness of the instructions for collection of the urine samples*

	N	per cent
Fasting	1441	98.8
Thirsting	1446	99.2
Micturition directly in the test tube	1418	97.2
Urine sample chilled	1365	93.6
Incubation time in the bladder > 4 hours	1431	98.0
Incubation time in the bladder > 8 hours	1392	95.4
Total number and percentage following the instructions in all respects	1283	88 6

who had followed the instructions are shown in Table 2.

Of the 55 children who had growth of more than 10^5 microorganisms/ml of urine in their first samples the bacteriological results were reproduced in 22. Thus these children, all girls, had significant bacteriuria, which gives a prevalence of 1.5 per cent among the girls. The remaining 33 children were followed with repeated examinations during several months, but the bacteriological findings were not reproducible. Repeated samples from the 524 children with growth of < 10^4 or 10^4—10^5 micro-organisms/ml of urine did not show significant bacteriuria in any case.

Uriglox®

For evaluation of the test paper Uriglox® in screening for significant bacteriuria the total material of 2016 children was considered irrespective of whether the instructions were followed or not. No color reaction of the test paper was considered as an indication of bacteriuria and a color reaction even if faint as normal. Out of the 2016 children, 22 were judged to have significant bacteri uria and of these the test paper disclosed all, i.e. the sensitivity of the test paper was 100 per cent. Among the 1991 children without significant bacteriuria, the test paper

53 THE UPTAKE OF BILIRUBIN IN HUMAN ERYTHROCYTES

D BRATLID

From the Paediatric Research Institute Rikshospitalet Oslo Norway

It has been known that bilirubin can be extracted from erythrocytes of icteric new borns. Different workers have found that 100 ml human erythrocytes can bind approximately 3 mg bilirubin and this has been given some importance in exchange transfusions.

The binding between bilirubin and erythrocytes was studied by incubating washed human erythrocytes with solutions of bilirubin and albumin in Krebs-Ringer-Glucose pH 7 4 It was found that binding to the erythrocytes increased markedly when the molar bilirubin/albumin ratio in the incubate exceeded 1 1 This increase seems to be related to the binding capacity of albumin for bilirubin. The binding of bilirubin was also dependent on the bilirubin concentration in the medium. With a concentration of bilirubin of 20 mg/100 ml and a molar ratio of 2/1 human erythrocytes were found to bind as much as 10 mg bilirubin/100 ml erythrocytes. It therefore seems that binding only to the erythrocyte membrane cannot fully explain the findings, and intracellular uptake of bilirubin must be considered.

The effect of pH on the uptake of bilirubin was then studied. When the pH of the incubate was varied from pH 7 4 to 7 0 the uptake of bilirubin increased markedly Adding salicylic acid and sulfisoxazole, which are thought to compete with bilirubin for the site on albumin, also markedly increased the cellular uptake of bilirubin This may be of some importance in the pathogenesis of kernicterus.

54 SCREENING FOR BACTERIURIA WITH URIGLOX® IN CHILDREN

L KÖHLER, H FRITZ and B. SCHERSTÉN

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Bacteriuria fulfils the requirements that may motivate a directed health control the frequency is high, more than 1 per cent, the prognosis is often serious, standardized diagnostic procedures are available as well as effective therapy

The only method of diagnosing bacteriuria to-day is with quantitative bacteriological culture In a mass screening program this procedure is, however time consuming expensive and unpractical. For this reason several other methods have been developed, chemical ones like Nitrite- Catalase- TTC-tests and simplified bacteriological ones like dip-inoculation-tests. Common to these methods is the fact that they do not satisfy the demands of both reliability and technical simplicity

For some years we have tested a new method of screening for bacteriuria, based on the ability of bacteria to consume the small amounts of glucose normally present

in the urine. In the case of bacteriuria there will be subnormal levels of urinary glucose. These small amounts may be determined quantitatively by sensitive chemical methods or qualitatively by a test paper URIGLOX®

This study reports the results of URI GLOX® as a screening method for bacteri uria among 2016 children, aged 4—19 years.

METHODS

The study is part of general health control, partly of 4-year-old children (449 girls and 499 boys) and partly of schoolgirls (1065 girls).

The urine samples were collected t home under standardized conditions. The midstream morning specimen was voided without prior periurethral cleansing directly into the sterile testube after 4—6 hours retention of urine in the bladder.

N eating or drinking was allowed during the night. The sample was chilled with ice cubes m plastic bag and delivered during the day to the laboratory for bacteriological culture and testing with URIGLOX®

All cultures showing growth of any organism considered to be pathogenic for th urinary tract as well as any pathological reaction of the test paper led to the collection f new samples. Generally repeated samples were requested until two consecutive samples were normal.

RESULTS

Instructions

The effectiveness of the instructions was recorded in detail *for the first 1459 children* examined. For the remaining 854 children, the retention time only was noted. Almost 90 per cent of the children followed the instructions in all respects (Table 1). In none of the children not following the instructions was significant bacteriuria demonstrable in additional samples.

Bacteriology

The results of the bacteriological cultures of the first samples from the 1847 children who had followed the instructions are shown in Table 2.

Table 1. *Effectiveness of the instructions for collection of the urine samples.*

	N	per cent
Fasting	1441	98.6
Thirsting	1448	99.2
Micturition directly in the test tube	1418	97.2
Urine sampl chilled	1366	93.6
Incubation time in the bladder > 4 hours	1431	98.0
Incubation time in the bladder > 8 hours	1392	95.4
Total number and percentage following the instructions in all respects	1293	88.6

Of the 55 children who had growth of more than 10^5 microorganisms/ml of urine in their first samples the bacteriological results were reproduced in 22. Thus these children, all girls, had significant bacteriuria, which gives a prevalence of 1.5 per cent among the girls. The remaining 33 children were followed with repeated examinations during several months, but the bacteriological findings were not reproducible. Repeated samples from the 524 children with growth of $< 10^4$ or 10^4—10^5 micro-organisms/ml of urine did not show significant bacteriuria in any case.

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Table 2. *Bacteriological findings in the first-collected specimens of 1847 children.*

Organism	Number of subjects with				Total
	No growth	$< 10^3$	10^3—10^5	$> 10^5$	
No growth	1268				1268
Urinary pathogens		118	144	35	297
Urinary nonpathogens		220	42	20	282
Total	1268	338	186	55	1847
Per cent	68.6	18.3	10 1	3 0	100

Table 3 *Evaluation of Uriglox® in screening for significant bacteriuria in 2016 children aged 4—19 years*

Screening results	Number of subjects with		Total
	Significant bacteriuria	No significant bacteriuria	
No color (Indication of bacteriuria)	22	12	34
Normal green color	0	1982	1982
Total number of children	22	1994	2016
Evaluation Sensitivity 100 % Specificity => 99 %			

gave a color reaction for 1979 (> 99 per cent) and thus a false indication of bacteriuria in less than 1 per cent (Table 3)

CONCLUSIONS

The study has shown that the test paper Uriglox® provides a reliable means of screening for bacteriuria in children. The sensitivity of the method in detecting bacteriuria was 100 per cent and the specificity was 99 per cent in disclosing nonbacteriurics.

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55 STUDIES OF ANTIBODIES AND IMMUNOGLOBULIN LEVELS IN URINE FROM CHILDREN WITH URINARY TRACT INFECTIONS CAUSED BY E. COLI

U JODAL, L. A. HANSON J HOLMGREN and B KAIJSER

From the Departments of Immunology and Bacteriology at the Institute of Medical Microbiology and Department of Paediatrics, University of Gothenburg Gothenburg Sweden

The existence of a local immune response in the urinary tract during infection has been shown by Sanford's group (1) Locally formed antibodies may also appear in human urine since it contains secretory IgA, which is usually locally produced. We wanted to study in the urine the levels of various immunoglobulins as well as specific anti

ies to the infecting *E.coli* strain during course of a urinary tract infection.

Passive hemagglutination with the O anti of the infecting *E. coli* strain was used analyses of urine samples concentrated - to 1,000-fold by ultrafiltration. In three eight children with a first attack of elonephritis and in all fourteen of those th a recurrent attack antibodies were und. There was no consistent correlation tween serum and urine antibody titres. ine from eight children without any history signs of urinary tract infection were also vestigated using a pool of *E. coli* O antigens r sensitization of sheep red cells (2). No tibodies were found in these individuals. In immunofluorescence studies the urinary tibodies all seemed to belong to the IgG ass.

Determinations of IgG IgA, IgM and bumin in urine was performed with the ngle radial immunodiffusion method of Mancini *et al.* (3) The IgG IgA and albumin vels were about five times higher in the rines from those who had a recurrent in-ection than in the normals. IgM was only und inconsistently

The validity of these determinations with the Mancini technique is dependent upon the availability of a corresponding homogeneous standard employed for the quantitation. In urine is present 11S secretory IgA as well as 7S IgA, which due to their dif ferences in size will have different diffusion constants and therefore will need separate standards.

A radial immuno-gel filtration method was developed which permitted separation and simultaneous quantitation of the two types of IgA. The variation in the proportions of 7S to 11S IgA observed in our patients suggests that quantitations of IgA in urine with the Mancini technique may often give erroneous results.

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56. SURVEILLANCE OF ACUTE VIRAL RESPIRATORY DISEASES IN CHILDREN

LEENA VIHMA

From the Department of Virology and Children Hospital, University of Turku, Turku, Finland

Acute respiratory infections in patients in children's hospitals and outpatient clinics in many countries have been carefully studied. The respiratory cases in children have been recorded in several longterm family studies. In well defined groups of children, e.g. in residential nurseries and in children's homes, the acute respiratory infections have been studied both during epidemics and for longer periods. Even children in some general and paediatric practices have been studied for acute respiratory infections, sometimes concurrently with a hospital series.

In this 2 year surveillance, the significance

of respiratory syncytial (RS) parainfluenza influenza and adenoviruses in the *etiology of acute respiratory disease* in children was evaluated and the value of a group of institutionalized children as an index of respiratory disease among children in the surrounding community was studied The population in the two study groups consisted of 40 families including at least one infant *and of infants residing in a small nursery in* the same city

In the infants of the nursery group the rate of respiratory illnesses was 6 3 per person year In the infants of the family group the illness rate 2.5 *per person year* was only about one-third of the rate in the nursery The rates observed in this study differed greatly from the rates found in some other studies. The commonly reported inverse relation of respiratory illness rate and age was also observed in this study

The highest incidence of acute respiratory *illnesses occurred in the fall* and the spring and an unexpectedly low incidence was observed in the family group during the frost period in midwinter This pattern of acute respiratory illnesses did not resemble *the pattern generally observed elsewhere in* other geographic regions for acute respiratory illnesses, with high fall and winter peaks

Specific virus etiology was established in 40 per cent of the 410 illnesses in the family group and in 31 per cent of the 188 illnesses in the nursery group RS virus was observed as an etiologic agent in 11 to 14 per cent of the respiratory *illnesses among the in* fants and children of the family group and in 7 per cent of the illnesses in the infants of the nursery group Parainfluenza viruses were observed in 7 to 11 per cent in the family group in the infants of the nursery group the rate was lower

In the family group parainfluenza virus types 1,2 and 3 occurred *in the ratio usually* observed. Influenza A2 infections occurred only in one-tenth of the families, representing 2 to 7 per cent of the respiratory illnesses.

Acute respiratory illnesses associated with *infections of adenovirus types 1—7* were observed in this long term study in a rate hitherto only reported to occur during adenovirus epidemics. In this series, in the infants of the nursery group an adenovirus infection was detected in 18 6 per cent of the acute respiratory illnesses. Adenovirus type 5 was prevalent, and infections with types 1 and 2 were also frequent. In some cases, adenovirus infections were observed *concurrently with RS virus infections.* In the infants of the family group adenoviruses were associated with 12.5 per cent of the *acute respiratory illnesses.* Double infections with RS and parainfluenza virus infections were observed. In children aged 2—6 years 17 per cent of the respiratory illnesses were associated with adenoviruses. In the family group types 1 and 5 were the commonest in infants, and types 7 and 2 in the children aged 2—6 years. In the older family children *infections due to type 3 were frequently* observed.

In the outbreaks of an acute respiratory illness identical etiology was seen only once, when the parainfluenza virus type 2 was *simultaneously prevalent as a sudden out* break in both groups. RS virus infections occurred in outbreaks, in the family group during both fall periods but in the nursery only one outbreak occurred in the second winter when all the infants contracted the RS infection. Once in both infant groups the occurrence of illnesses associated with adenoviruses was observed at the same time. The outbreaks of adenovirus types 2, 5 and 7 were not correspondingly observed in the family group Outbreaks due *to other* parainfluenza viruses, influenza A2 and Coxsackie B type 2 in the family group were not noticed in the infants of the nursery group. In both groups, in a third of the outbreaks the etiology remained totally unknown.

The clinical observations further empha sized the importance of these viruses in the

respiratory disease of children. Among the infants of the nursery RS virus and parainfluenza viruses were found to cause involvement of the lower respiratory tract more often than the unknown etiologic agents. Adenovirus infections were mainly associated with upper respiratory tract infections. The illnesses with detected virus etiology were more often febrile than the illnesses of unknown etiology This was due to RS and parainfluenza virus infections in the nursery group, but in the infants of the family group most of the adenovirus infections were likewise febrile. Febrile illnesses were certainly more readily reported in the family group than minor illnesses without fever Otitis media was often found in RS virus infections. The duration of all acute respiratory illnesses was longer in the infants of the nursery group than in infants of the family group.

In conclusion, it can be pointed out that the infants of the nursery represented a group with a high respiratory illness rate characterized by frequent adenovirus infections. Only occasionally did the viruses causing acute respiratory illness in the family children invade the nursery at the same time. Accordingly such isolated nurseries are not representative index populations for the acute respiratory illnesses in the surrounding community By a surveillance of even a small group of families more virus infections can be detected, and such a group probably more nearly reflects the epidemiologic pattern of acute viral respiratory infections in a community

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57 VARICOCELE IN CHILDREN AND ADOLESCENTS

J ØSTER

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The incidence of varicocele was investigated in an unselected material consisting of 1072 Danish schoolboys aged 6—19 years. No cases of varicocele were encountered among 188 boys aged 6—9 years, while the incidence among the 837 boys aged 10—19 years examined was 16.2 per cent. This showed a steadily increasing tendency from 5.7 per cent in the ten-year-old group to 19.3 per cent at the age of 14 years. The incidence of »genuine» clinical varicocele showed an increase from 1.9 per cent in ten-year-olds to 10.6 per cent in 14-year-olds. All of the varicoceles were localized to the left half of the scrotum.

The development of puberty was more advanced in the boys with varicocele than in the control material, and boys with varicocele were taller than those without varicocele. These two observations are presumed to be of significance for the development of varicocele.

of respiratory syncytial (RS) parainfluenza, influenza and adenoviruses in the etiology of acute respiratory disease in children was evaluated and the value of a group of institutionalized children as an index of respiratory disease among children in the surrounding community was studied. The population in the two study groups consisted of 40 families including at least one infant and of infants residing in a small nursery in the same city

In the infants of the nursery group the rate of respiratory illnesses was 6.3 per person-year In the infants of the family group the illness rate 2 5 per person year was only about one-third of the rate in the nursery The rates observed in this study differed greatly from the rates found in some other studies The commonly reported inverse relation of respiratory illness rate and age was also observed in this study

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In the family group parainfluenza virus types 1 2 and 3 occurred in the ratio usually observed. Influenza A2 infections occurred only in one-tenth of the families, representing 2 to 7 per cent of the respiratory illnesses.

Acute respiratory illnesses associated with infections of adenovirus types 1—7 were observed in this long term study in a rate hitherto only reported to occur during adenovirus epidemics. In this series, in the infants of the nursery group an adenovirus infection was detected in 18 6 per cent of the acute respiratory illnesses. Adenovirus type 5 was prevalent, and infections with types 1 and 2 were also frequent. In some cases, adenovirus infections were observed concurrently with RS virus infections. In the infants of the family group adenoviruses were associated with 12.5 per cent of the acute respiratory illnesses. Double infections with RS and parainfluenza virus infections were observed In children aged 2—6 years 17 per cent of the respiratory illnesses were associated with adenoviruses. In the family group types 1 and 5 were the commonest in infants, and types 7 and 2 in the children aged 2—6 years. In the older family children infections due to type 3 were frequently observed.

In the outbreaks of an acute respiratory illness identical etiology was seen only once, when the parainfluenza virus type 2 was simultaneously prevalent as a sudden out break in both groups. RS virus infections occurred in outbreaks in the family group during both fall periods but in the nursery only one outbreak occurred in the second winter when all the infants contracted the RS infection. Once in both infant groups the occurrence of illnesses associated with adenoviruses was observed at the same time The outbreaks of adenovirus types 2, 5 and 7 were not correspondingly observed in the family group Outbreaks due to other parainfluenza viruses, influenza A2 and Coxsackie B type 2 in the family group were not noticed in the infants of the nursery group In both groups, in a third of the outbreaks the etiology remained totally unknown.

The clinical observations further empha sized the importance of these viruses in the

bronchial asthma but also patients with chronic bronchitis and chronic emphysema of more or less unknown etiology The results of such studies are difficult to evaluate.

In the investigation by Irnell of the haemodynamic function of adult asthmatics, patients with other chronic diseases were ruled out (5). Irnell found the right atrial pressure and the pressure in the pulmonary artery to be normal. There were no definite signs of cor pulmonale in any of the 69 patients studied.

In children with bronchial asthma cor pulmonale is very seldom noted (2), which agrees with our results from electrocardiographic investigations of asthmatic children during physical exercise.

Postmortem findings after death in acute asthma. Right-sided cardiac failure during an attack of asthma seems to be a risk in older asthmatics with previous development of emphysema (1). In young adults and children, necropsy findings of such failure are seldom met (6, 7) In the study by Speizer et al. there were only four cases of 113 with signs of pulmonary oedema (7).

Haemodynamic investigations during an attack of asthma have been performed in adult asthmatics (4) An increase of pressure in the pulmonary artery was found. Furthermore, the pressures in the pulmonary artery and left atrium varied synchronically with respiration. The increased pressure noted in the left atrium during expiration caused decreased venous return to the heart and concomitant decreased stroke volume. This may imply a risk of forward failure» during an attack of severe asthma. The hearts of children and young adults probably resist this strain better than older adults.

Further factors influencing the heart during acute asthma are possible disturbances of electrolyte balance (e g hypokalemia), acid-base balance and arterial oxygenation.

Heavy medicinating with adrenaline-like substances e.g. isoprenaline as difficult dosable inhalation should also be considered (7) Digatalization in patients with cor puolmonale may sometimes be a hazard (3) and in acute asthma with possible concomitant abnormalities of the electrolyte pattern digitalization is risky Disturbances of homeostasis and intoxications can separately or together cause cardiac arrythmias.

Cardiac arrest has been mentioned as an explanation of sudden death in children with acute asthma.

CONCLUSIONS

Cardiac failure in children with acute, severe asthma seems to be an unusual complication. Cardiac arrythmias may develop and should be considered during the treatment of a status asthmaticus. Treatment of acidosis, hypercapnia, hypoxia and abnormalities in electrolyte balance is the primary prophylaxis against cardiac complications. Digitalization should not be used routinely

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SESSION B II

STATUS ASTHMATICUS

CHAIRMAN ALF BACKMAN

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58 STATUS ASTHMATICUS

Introduction

A. BACKMAN

From the Children s Hospital University of Helsinki, Helsinki, Finland

59 CLINICAL PICTURE IN ACUTE ASTHMA OF CHILDREN

K. WILKEN-JENSEN

From the Department of Paediatrics and Department of Children s Allergy University Hospital, Copenhagen, Denmark

60 PATHOPHYSIOLOGY IN ACUTE ASTHMA OF CHILDREN

INGA ENGSTRÖM

From the Paediatric Clinic St. Gorans Hospital, Stockholm, Sweden

61 CARDIAC STATUS IN ACUTE ASTHMA OF CHILDREN

B KJELLMAN

From the University Hospital of Lund, Lund, Sweden

There are very few direct data on the condition of the heart in children with an acute attack of asthma. The problem must, therefore be tackled indirectly

Cardiac status in asthmatics during a remission. As a rule studies of the cardiac function in adults with bronchobstructive disease include not only patients with pure

bronchial asthma but also patients with chronic bronchitis and chronic emphysema of more or less unknown etiology The results of such studies are difficult to evaluate.

In the investigation by Irnell of the haemodynamic function of adult asthmatics, patients with other chronic diseases were ruled out (5). Irnell found the right atrial pressure and the pressure in the pulmonary artery to be normal. There were no definite signs of cor pulmonale in any of the 60 patients studied.

In children with bronchial asthma cor pulmonale is very seldom noted (2) which agrees with our results from electrocardiographic investigations of asthmatic children during physical exercise.

Postmortem findings after death in acute asthma. Right-sided cardiac failure during an attack of asthma seems to be a risk in older asthmatics with previous development of emphysema (1). In young adults and children, necropsy findings of such failure are seldom met (6, 7). In the study by Speizer et al. there were only four cases of 115 with signs of pulmonary oedema (7)

Haemodynamic investigations during an attack f asthma have been performed in adult asthmatics (4). An increase of pressure in the pulmonary artery was found. Furthermore, the pressures in the pulmonary artery and left atrium varied synchronically with respiration. The increased pressure noted in the left atrium during expiration caused decreased venous return to the heart and concomitant decreased stroke volume. This may imply a risk of forward failures during an attack of severe asthma. The hearts of children and young adults probably resist thus strain better than older adults.

Further factors influencing the heart during acute asthma are possible disturbances of electrolyte balance (e.g. hypokalemia), acid-base balance and arterial oxygenation.

Heavy medicinating with adrenaline-like substances e.g. isoprenaline as difficult-dosable inhalation should also be considered (7). Digatalization in patients with cor puolmonale may sometimes be a hazard (3) and in acute asthma with possible concomitant abnormalities of the electrolyte pattern digitalization is risky. Disturbances of homeostasis and intoxications can separately or together cause cardiac arrythmias.

Cardiac arrest has been mentioned as an explanation of sudden death in children with acute asthma.

CONCLUSIONS

Cardiac failure in children with acute, severe asthma seems to be an unusual complication. Cardiac arrythmias may develop and should be considered during the treatment of a status asthmaticus. Treatment of acidosis, hypercapnia, hypoxia and abnormalities in electrolyte balance is the primary prophylaxis against cardiac complications. Digitalization should not be used routinely

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62. TREATMENT IN ACUTE ASTHMA OF CHILDREN

S. KRAEPELIEN

From the Allergy Department, Sachs' Children's Hospital, Stockholm, Sweden

63 INTENSIVE CARE IN STATUS ASTHMATICUS

H. FEYCHTING

From the Paediatric Clinic, St. Görans Hospital, Stockholm Sweden

64 NITROUS OXIDE IN THE TREATMENT OF STATUS ASTHMATICUS

T SUUTARINEN

From the Children's Hospital, University of Helsinki, Helsinki, Finland

Inhalation of nitrous oxide–oxygen mixtures for the treatment of acute attacks of bronchial asthma was advocated as early as 1870 and 1881 but the therapeutic value of this technique has remained unexploited for almost a century

In 1960 Smolinskii reported a study of the use of nitrous oxide in 108 patients with bronchial asthma, in which a large number of the patients were treated at home. Otherwise the use and value of nitrous oxide in the treatment of bronchial asthma is little known in the medical literature

At the Children's Hospital of the University of Helsinki, nitrous oxide and oxygen mixtures have been used in the treatment of status asthmaticus in about 10 patients over the past 2 years. Initially the patients were intubated, relaxed and ventilated with an Engström respirator using various mixtures of nitrous oxide, oxygen and air but more recently the nitrous oxide-oxygen mixture has also been administered through an ultrasonic nebulizer into an oxygen tent.

65 GLUCAGON IN STATUS ASTHMATICUS

A. KOIVIKKO

From the Children's Hospital, University of Turku, Turku, Finland

66. IgE SPECIFIC REAGINS DURING HYPOSENSITIZATION

T BERG and S. G O. JOHANSSON

From the Department of Paediatrics and the Blood Center University Hospital, Uppsala, Sweden

In a number of children hypersensitive to pollen with symptoms of asthma or allergic rhinitis, the serum concentrations of specific IgE antibodies (reagins) and total IgE were followed during and after rush hyposensitization. The reaginic activity in serum was determined by the radioallergosorbent technique (RAST) The hyposensitization was performed at the hospital over a period of 5—7 days with simultaneous injections of different pollen allergens in children allergic to various kinds of pollen. Serum samples were taken at the start of the treatment and daily during the childrens' stay in hospital. A new sample was taken 1—2 weeks after discharge from hospital when the children came back to get their maintenance dosages.

In agreement with the finding of an earlier investigation, the hyposensitization gave rise to increasing IgE levels in serum in the majority of children. The concentration of specific antibodies of the IgE type also increased in most of the children. At the control 2—3 weeks after the start of the treatment, a pronounced increase of the serum reaginic activity was found in some cases. One of the treated children had about ten times the initial concentration of specific reagins 3 weeks after the beginning of hyposensitization.

During the very first days of treatment the concentration of reaginic antibodies in serum increased rapidly in some cases while in other cases there was only a slow increase or no change at all. In children hyposensitized with different pollen allergens a similar development of the different IgE antibodies was often found. However there was no parallelism as a rule between the development of specific reagins on one hand and that of total IgE on the other

67 IMMUNOLOGICAL DEFICIENCY STATES IN INFANTS

P J MOE, J O. LAMVIK and B. LARSEN

From the Department of Paediatrics, Department of Pathology and Department of Microbiology, University of Bergen, Bergen, Norway

Immunological deficiency diseases in infants may be divided into three groups:

1. The Swiss type of hypogammaglobulinaemia, characterized by thymic dysplasia, depletion of small lymphocytes in lymphoid organs and blood, and reduced amounts of serum immunoglobulins, first described by Glanzmann & Riniker (1950). In this disorder cellular as well as humoral immunity is usually markedly impaired, although some cases have been reported showing no definite reduction of immunoglobulins.

2. Congenital, sex-linked hypogammaglobulinaemia with markedly reduces amounts of serum immunoglobulins, but without definite impairment of cellular immune reactions, first described by Bruton in 1952.

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3. A miscellaneous group of immunological

deficiency states, sometimes secondary to malignant or inflammatory changes in the lymphoid organs.

Three cases of thymic dysplasia, one case of sex linked hypogammaglobulinaemia and 7 cases belonging to the miscellaneous group have been treated in the last 6 years at the Children's Hospital in Bergen. All three cases of thymic dysplasia died from severe infections despite antibacterial treatment. A sister of one of the cases had previously died from septicaemia. The family history of the others and serum immunoglobulin determinations in the parents and healthy siblings disclosed no abnormality The case of Bruton's type and the 7 cases of the miscellaneous group have not represented any great therapeutic problem so far

SESSION C II

PAEDIATRIC EDUCATION IN SCANDINAVIA

CHAIRMEN *NIILO HALLMAN and GÖRAN STERKY*

PROGRAMME

I. GRADUATE EDUCATION

a) Comments to abstract on present situation

b) Information.

1) Two years experience of multiple choice questions as part of examination (Sterky)

2) Absolute *versus* relative grading (Kjellman)

3) A self instructing teaching programme The somatic and psychomotor development of the child (Lagerkvist)

c) Objectives. Introduction (Bödtker-Henriksen, Petersson and Wallgren) Discussion

II. POSTGRADUATE EDUCATION

a) Present situation and planning Introduction (Lindquist, Melchior Moe, Tryggvason and Wasz Höckert)

b) Discussion. Collaboration within Scandinavia

III. CONTINUING EDUCATION

a) Report by secretaries of courses (*held 69—70*) (Aas, Braestrup and Sterky)

b) Plannings by Scandinavian Commitee (Rinvik)

c) Discussion

68. SELF INSTRUCTING TEACHING PROGRAMME THE SOMATIC AND PSYCHOMOTOR DEVELOPMENT OF THE CHILD

B. LAGERKVIST

From the Paediatric Clinic St. Görans Hospital, Stockholm, Sweden

A self-instructing teaching programme has been designed (1) and tested on medical students during their paediatric training. This form of teaching has seldom been used previously in medical education. This is the first time it will be used in a *clinical* subject in Scandinavia. Bernmalm (2) amongst others has reported that a self instructing teaching

programme is more effective than conventional teaching. A greater amount of material is learned in a shorter time and knowledge is retained longer in the mind of the student.

Four different reasons influenced the choice of subject matter

1 The basic facts that exist about the development of the child are not questioned by medical scientists. The amount of knowledge in the programme may therefore be considered constant and will not need changing during the next few years.

2. The normal development of the child is a section that is clearly defined and is necessary as the basis of paediatric instruction.

3 In this subject matter terms and definitions may be difficult to find in conventional textbooks and are used in different ways by different authors. A comprehensive reappraisal of the terminology used is certainly indicated.

4 Each paediatric curriculum begins with 2—4 lectures on the development of the child. These lectures may instead now be used for instruction in other subjects, or devoted to clinical examples of normal and pathological stages of development.

When working on the programme the method has been the following. The field of the subject has been divided into a number of large sections. They have then been subdivided into subsections which are of convenient size for lecturing upon at any one time. The contents of these are fairly independent of one another.

Then we have limited the extent of the subject matter by making a number of test problems. They are to cover the field of the subject completely. When answering them the student is compelled to use all the information given in the programme. The test problems have been sent to another University Clinic to unify the amount of knowledge at different institutions. After this the programme has been prepared.

Table 1 *Result of the written test.*

Score	Number of medical students
35—36	29
33—34	16
31—32	10
28—30	2
25—27	2
Less than 25	2

In connection with the above mentioned subsections, revision problems have been designed. They are used by the student to test how much he has understood and learnt from the subdivisions previously studied.

When testing the programme the students had to pass a written test and answer two questionnaires. The first was about the actual material and the second about their opinion of self instructing teaching programmes within a clinical subject. The written test was comprised of 36 questions which were taken directly from the 110 test problems in the programme. 61 medical students took part in the test. The effectiveness of the programme is shown in Table 1.

Almost one half of the participants had none or one error and a little more than 2/3 had not more than three errors.

From the first questionnaire it was clear that the programme was very well accepted by the students. More than 3/4 of them said that it was both more effective and less stressing than conventional teaching methods. Approximately 1/2 of the students said it was more interesting to read. From the students point of view the most important advantages are quicker teaching and a greater concentration on the most relevant subject matter. The average time spent on the programme was 3—5 hours. An observation obtained from the second questionnaire was that the method tended to give a more mechanical and uncritical education with less application of the subject matter.

The programme can be used without any previous knowledge of paediatrics. It can

suitably be used as an introduction to the paediatric training of students and be studied without supervision. Naturally clinical introduction in combination with this teaching method is obviously preferable. The content of this programme is basic. It is of importance for nearly everyone working with the care of children in health and disease. The programme might also be used even in the education of children s nurses, and in the postgraduate training of nurses and doctors working with children who are not paediatricians.

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PLENARY SESSION III

PERINATAL INFECTIONS

CHAIRMAN LARS A. HANSON

Symposium on Perinatal Infections

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69 DEFENCE AGAINST INFECTIONS IN THE PERINATAL PERIOD

L. A. HANSON

From the Department of Immunology Institute of Medical Microbiology and Department of Paediatrics University of Gothenburg Gothenburg Sweden

Man is constantly exposed to microorganisms which would invade him and cause infection and *disease if* it were not for his defence mechanisms. Usually there is a balance between the various virulence factors of the many aggressors and the multiple components of the host s defence against infection. In the »compromised host the defence mechanisms are deranged by for example undernutrition, debilitating disease or immunosuppressive therapy This gives the aggressors a much greater chance to cause infection and disease

To some extent the fetus and the neonate can be regarded as a compromised host» since all the defence mechanisms are not yet fully developed at a time when exposure to aggressors can or will occur The defence against infection consists of a complicated interplay between many components. The ontogenetic development of some but not all of these have been investigated. Thus among the nonspecific components it is known for example that lysozyme can be demonstrated in most fetuses after about 20 weeks of gestation, that newborns are usually deficient in serum complement, and that the bacterial function of polymorphonuclear leucocytes may be deficient — although there are some controversial data concerning this last point.

The specific components of the defence against infection, the two effector mechanisms of the immune response the humoral antibodies and the committed lymphocytes, have been investigated by several authors. It is thus well known that maternal IgG is actively transported via the placenta to the fetus, resulting in a somewhat higher level of IgG in the cord blood than in the maternal serum. During the latter part of gestation the fetus also has a capacity to synthetize small amounts of IgG and IgM. The neonate seems be able to give an antibody response to several antigens. This antibody response may be somewhat different from that of the adult, but has not been studied in greater detail for very many antigens.

The ontogeny of the cell mediated immunity is less well known, but recent studies indicate that functional lymphocytes may be present from the 15th to the 18th week of gestation. The most basic question, how and

when the fetus or neonate obtains the capacity to respond against the tens of thousands of antigens present in the milieus has not yet been fully elucidated. When can we expect to get an immune response against all possible microorganisms, comparable to that of the adult as regards, for example, immunoglobulin class, amount or affinity of antibodies as well as number and efficiency of committed lymphocytes? A few answers are already available from clinical experience, but it is obvious that much more information is needed before we can evaluate all the defence mechanisms functioning during the perinatal period. Thus, not even the possible importance of milk has been finally clarified in man. Although no transfer of immunoglobulins to the infant's circulation via milk has been shown there is some evidence that milk may provide a local protection of importance in the gastrointestinal tract.

The fact that the fetus and the neonate may be regarded as a »compromised host» is illustrated by the special pattern of infectious diseases appearing in the perinatal period. This is exemplified by the following papers in this symposium. The special circumstances in developing countries where additional factors like undernutrition and poor hygiene may further change the balance in favour of the aggressors is also described. Finally the therapeutic problems posed by infectious diseases in the perinatal period are discussed.

70 MICROORGANISMS CAUSING PERINATAL INFECTIONS BACTERIA STAPHYLOCOCCI, PSEUDOMONAS, KLEBSIELLA

O. PETTAY

From the Children' Hospital, University of Helsinki, Helsinki, Finland

71 MICROORGANISMS CAUSING PERINATAL INFECTIONS E. COLI

J. WINBERG

From the Paediatric Clinic, St. Görans Hospital, Stockholm, Sweden

72 MICROORGANISMS CAUSING PERINATAL INFECTIONS VIRUS RUBELLA

J. LEERHØY

From the State Serum Institute Copenhagen, Denmark

Rubella is reviewed with respect to newer concepts of (1) the rubella syndrome, (2) risks to the fetus following intrauterine infection, (3) laboratory diagnosis, and (4) preventive measures.

(1) Malformations of the fetus caused by

maternal rubella are generally referred to as the rubella syndrome The classical rubella syndrome comprises malformations of the eye (cataract, microphthalmia) cardiac defects (patent ductus arteriosus and other defects) and damage to the inner ear (deafness) Recent clinical and virological examinations of children born after rubella in utero show however that hepatosplenomegalia, generalized purpura, thrombocytopenia, encephalomyelitis, low birthweight and radiologically distinctive changes of the bones may also be included in the rubella syndrome. Further histo-pathological examinations of fetuses aborted after maternal rubella have shown changes in the heart, liver kidney eye ear and other organs.

Infants with the rubella syndrome are found to excrete rubella virus for as long as 12 to 18 months after birth, being thus a source of infection to non immune individuals. This postnatal shedding of virus is remarkable from an immunological viewpoint since it occurs in the presence of specific rubella antibody often in high titre.

(2) The risk of malformations caused by intrauterine rubella infection may vary from year to year but it is presumably greater than previously anticipated According to recent reports in the literature the risk following maternal rubella in the first trimester may be as high as 25 to 35 per cent. Gross malformations seem to appear only after maternal rubella in the first three months of pregnancy while rubella in the fourth month probably results in only slight damage to hearing

(3) Among several serological methods presently available for laboratory diagnosis of rubella the haemagglutination-inhibition test appears to be the best for routine purposes. It is based on titration of specific antibody in paired blood samples drawn from the patient in the acute phase of disease and one to two weeks later The importance of obtaining the first blood sample as soon as possible after the appearance of rash or after exposure is emphasized. Isolation and identification of rubella virus, e.g from throat swabs, may also be employed to establish the diagnosis.

(4) The administration of human gamma-globulin has for many years been generally recommended for treatment or prevention of rubella during pregnancy The prophylactic effect of gamma globulin must, however be regarded as uncertain, though it is not yet fully elucidated. Preliminary trials with live rubella vaccines have shown good antibody response and although virus may be shed from the nasopharynx of vaccinees for a few weeks after vaccination, transmission of infection to susceptible contacts seems to be negligible The unknown teratogenicity of the attenuated virus strains used for vaccine production prohibits the vaccination of pregnant and potentially pregnant women and may represent a problem for routine vaccinations.

In many countries rubella in the early stages of pregnancy is recognized as a legal indication for therapeutic abortion and until rubella can be controlled by vaccination, this seems to be the only means available to prevent the birth of infants suffering from rubella malformations.

73 MICROORGANISMS CAUSING PERINATAL INFECTIONS VIRUS CYTOMEGALOVIRUS

O PETTAY

From the Children's Hospital, University of Helsinki, Helsinki, Finland

74. MICROORGANISMS CAUSING PERINATAL INFECTIONS TOXOPLASMA

E. LYCKE

From the Institute of Virology University of Gothenburg Gothenburg Sweden

75 PERINATAL INFECTIONS IN DEVELOPING COUNTRIES

L. ENGARDT

From the Ethio-Swedish Paediatric Clinic, Princess Tsahai Memorial Hospital, Addis Abeba, Ethiopia

The population of Ethiopia is estimated at around 23 millions. The vast majority are farmers. The hospitals are situated in a few major towns. There are only about 430 doctors, including about 350 foreign doctors. The majority of the doctors are working in the two major cities, Addis Abeba and Asmara. It is estimated that only about 15 per cent of the population is reached by modern medicine.

Marriage conditions are very loose compared to most Western countries. According to one study from Addis Abeba, 39 per cent of mothers who brought their children to a clinic were single (the majority however said they were divorced). Of the 61 per cent who were married, more than 50 per cent had one or more previous divorces behind them.

Hygienic conditions are poor especially in the cities. The normal house is made of wood-enforced clay with a roof of corrugated iron. Municipality water is not available to everybody few have tap water in their houses. There is no sewerage system and few of the poor have a latrine.

The vast majority of mothers deliver their children in the home. The »midwives» are usually older women, relatives or neighbours. No special precautions with regard to cleanliness are taken. In Addis Abeba the umbilicus is nowadays usually cut with a new razor blade, but in the rural areas an ordinary knife, a piece of broken glass, a sharp stone etc. is normally used. The umbilicus is covered with home-made, dirty butter The practice of applying cow's dung to the umbilicus, described in many other parts of Africa, appears to be almost non-existent in Ethiopia.

During the first day of life, butter is also put in the mouth and sometimes even in the nostrils of the baby This lubrication is usually repeated now and then during the first month of life.

Breastfeeding is the rule, at least during the first few months of life.

Forced feeding is a common practice. Expressed breastmilk or some substitute is poured into the cupped hand, the nostrils of the child are closed and the fluid forced into the mouth.

Circumcision is performed on practically all boys. Usually it is done on the 7th day of life. Female circumcision is also practiced. Either the labia minora or the clitoris are cut away The uvula is considered prone to grow downwards and suffocate the child. In almost all Ethiopian children the uvula is therefore cut, either prophylactically during the first month of life, or later when the child gets a throat infection. The operation is performed by unqualified »witchdoctors»

maternal rubella are generally referred to as the rubella syndrome The classical rubella syndrome comprises malformations of the eye (cataract, microphthalmia) cardiac defects (patent ductus arteriosus and other defects) and damage to the inner ear (deafness) Recent clinical and virological examinations of children born after rubella in utero show however that hepatosplenomegalia, generalized purpura, thrombocytopenia, encephalomyelitis, low birthweight and radiologically distinctive changes of the bones may also be included in the rubella syndrome Further histo-pathological ex aminations of fetuses aborted after maternal rubella have shown changes in the heart, liver kidney eye, ear and other organs.

Infants with the rubella syndrome are found to excrete rubella virus for as long as 12 to 18 months after birth, being thus a source of infection to non immune individuals This postnatal shedding of virus is remarkable from an immunological viewpoint since it occurs in the presence of specific rubella antibody often in high titre

(2) *The risk of malformations caused by* intrauterine rubella infection may vary from year to year but it is presumably greater than previously anticipated. According to recent reports in the literature the risk following maternal rubella in the first tri mester may be as high as 25 to 35 per cent. Gross malformations seem to appear only *after maternal rubella in the first three* months of pregnancy while rubella in the fourth month probably results in only slight damage to hearing

(3) Among several serological methods presently available for laboratory diagnosis of rubella the haemagglutination-inhibition test appears to be the best for routine purposes. It is based on titration of specific antibody in paired blood samples drawn from the patient in the acute phase of disease and one to two weeks later The importance of obtaining the first blood sample as soon as possible after the appearance of rash or after exposure is emphasized. Isolation and identification of rubella virus, e.g from throat swabs, may also be employed to establish the diagnosis.

(4) The administration of human gammaglobulin has for many years been generally recommended for treatment or prevention of rubella during pregnancy The prophy lactic effect of gamma globulin must, how ever be regarded as uncertain, though it is not yet fully elucidated. Preliminary trials with live rubella vaccines have shown good antibody response and although virus may be shed from the nasopharynx of vaccinees for a few weeks after vaccination, transmission of infection to susceptible contacts seems to be negligible. The unknown teratogenicity of the attenuated virus strains used for vaccine production prohibits the vaccination of pregnant and potentially pregnant women and may represent a problem for routine vaccinations.

In many countries rubella in the early stages of pregnancy is recognized as a legal indication for therapeutic abortion and until rubella can be controlled by vaccination, this seems to be the only means available to prevent the birth of infants suffering from rubella malformations.

73 MICROORGANISMS CAUSING PERINATAL INFECTIONS VIRUS CYTOMEGALOVIRUS

O PETTAY

From the Children's Hospital, University of Helsinki, Helsinki, Finland

PARALLEL SESSION C III a

NEUROLOGY CHILD PSYCHIATRY

CHAIRMEN BERTIL LINDQUIST and OLE WASZ HÖCKERT

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77 MALNUTRITION AND BRAIN DEVELOPMENT — NEUROPHYSIOLOGICAL OBSERVATIONS

G. ENGENER, IRENE SJÖGREN and R. VAHLQUIST

From the Department of Paediatrics, Uppsala, Sweden and the Ethiopian Nutrition Institute, Addis Abeba, Ethiopia

Severe malnutrition at an early age can lead to permanent stunting of physical growth. The brain manifests a very rapid growth and development at an early age. It is not surprising therefore, that also this organ may suffer. The results of animal experiments as well as of clinical observations prove that this is in fact the case.

The effects of malnutrition on brain growth and development have so far been investigated mainly with histological and biochemical methods. The authors will present preliminary results of investigations with neuro-physiological methods (echo-encephalography conduction velocity of peripheral motor nerves, transillumination). With these methods it is possible to perform — without any untoward reactions for the children — cross-sectional as well as longitudinal studies. The results to be presented originate from investigations on Ethiopian children with different degrees of malnutrition. They are part of the research activities at the SIDA supported Ethiopian Nutrition Institute.

78 SEX DIFFERENCES IN THE EEG OF NORMAL CHILDREN AND YOUNG PERSONS AGED 1 TO 21 YEARS

O. EEG-OLOFSSON and L. PETERSÉN

From the Department of Paediatrics, University of Gothenburg, Gothenburg Sweden

The evolution of the EEG in normal children and young persons has been studied. The material is selected according to clearly defined criteria of normality concerning prenatal, perinatal as well as postnatal history.

The total material comprises 928 individuals — 483 females and 445 males —

Nonerupted teeth especially the lower canines, are supposed to be the cause of diarrhoea, and are very often extracted with the help of primitive, unclean equipment. Available figures indicate that the average birth weight in Ethiopia is around 3 1 kg The frequency of low birth weight (< 2500 g) is about 8—9 per cent.

According to various surveys, the neonatal mortality (0—1 month) is around 70—100 per 1000 live births. The infant mortality (0—1 year) is around 170—200 per 1000 live births. Out of a total of 1815 admissions during 1969 to the Ethio-Swedish Paediatric Clinic in Addis Abeba 297 patients (13 6 per cent) were neonates (0—1 month) The total mortality in this age group was 40 per cent, as compared to an overall mortality of 18.8 per cent.

Among the 297 neonates, 140 infection diagnoses were registered. Among the children with prematurity and infection, the mortality was as high as 74.3 per cent. The two most common causes for both morbidity and mortality in this group were sepsis and gastroenteritis. Among the fullterm neonates with an infection, the mortality was 37 4 per cent. In this group tetanus neonatorum was the most common diagnosis, followed by lower respiratory tract infection, sepsis, gastroenteritis etc.

Because of its important role among infections in the neonatal period in developing countries, tetanus neonatorum is briefly discussed.

Congenital syphilis is another less dramatic, relatively common but probably underdiagnosed infection of the newborn. According to a recent study in Addis Abeba, 15.3 per cent of mothers delivered in an urban MCH centre were seropositive for syphilis and of their children 23 1 per cent remained positive when followed up 1—12 months later The clinical manifestations are briefly discussed.

76 PERINATAL INFECTIONS DRUG TREATMENT

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From the Department of Clinical Parmacology Karolinska Sjukhuset, Stockholm Sweden

Knowledge of the pharmacokinetic features of the patient is essential for successful treatment with antibiotics, since the patient's own pathways for transport and distribution are used in order to bring the drug to the locus of infection. Recent advances in paediatric pharmacology have demonstrated the pharmacokinetic uniqueness of the first few weeks of life. The processes of drug distribution metabolism and elimination are all influenced by age whereas absorption seems to be relatively age-independent. The net effect of maturation phenomena may be further influenced by the disease. Dosage schedules for the various ages may be useful but data reported in the literature suggest that individual variations in drug distribution in the neonate — as well as in the adult — may also strongly affect the clinical results of treatment. Ideally therefore, the plasma levels of all antibiotics should be followed in all newborn patients with severe infections.

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The amount of more or less conspicuously asymmetrical theta activity with no clear relation to drowsiness was found statistically significantly more in boys than in girls in the ages 1—8 years. In the ages 9—13 years there was no sex difference, while from 14 to 21 years there was a statistically significant preponderance for girls.

From 8 years onwards girls showed statistically significantly more paroxysmal responses to intermittent photic stimulation compared to boys. In these ages activation by intermittent photic stimulation was discontinued because of resulting effects significantly more in girls.

79 LONG-TERM FOLLOW UP OF CHILDREN WITH SEVERE EPILEPSY TREATED WITH CARBAMAZEPINE (TEGRETOL® GEIGY)

INGRID GAMSTORP

From the Department of Paediatrics Central Hospital, Jönköping Sweden

A trial to treat a selected group of epileptic children with carbamazepine (Tegretol® Geigy) was started in February 1963 The original group consisted of 58 children 55 of them were included because their epilepsy was difficult to control on drugs available, 2 because they had shown an allergic reaction to other drugs tried and in 1 carbamazepine was used as the first drug Of these 58 patients 30 showed a good initial response as 22 became entirely seizure-free (group A) and 8 experienced a reduction in the frequency of seizures by at least 75 per cent (group B) Six of the 30 patients relapsed in spite of continued treatment 4 to 12 months after the start of the trial. At the end of the observation period (February 1965) 19 patients remained in group A and 5 in group B (Gamstorp 1966)

These 24 patients have then been followed further Of the 19 patients in group A 13 remain entirely seizure-free. One of them was lost from follow up after 1½ years, the remaining patients have all been followed for at least 3½ years, 8 of them for more than 6 years. Three of these patients have stopped taking the drug after 5 years without seizures, a normal EEG and completed pubertal development with no relapse of seizures the remaining patients are still on the drug in spite of the long symptom-free period because they are still in the middle of puberty or have an abnormal EEG

Of the relapsing 6 patients 5 have mild and infrequent attacks and can thus be judged as belonging to group B All have been followed for at least 3 years, 4 of them for 5 to 6½ years they are all still on the drug One patient had a severe relapse 6 months after the initial response she was lost from follow-up after 3 years.

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in February 1965 3 still remain in this group. Time of follow up is 2, 5 /₂ and 6 years respectively One patient became entirely seizure-free one year after the start of therapy and has remained so she has thus moved from group B to group A. She has been followed for 5 /₂ years. One patient had a severe relapse 2¹/ years after the initial response he was followed for 6 months thereafter and continued to have frequent seizures.

Thus, of the 30 patients initially responding to carbamazepine, 6 relapsed during the first period of follow-up, i.e. within 4 to 12 months after the initial response. Of the remaining 24 patients 22 are well or considerably improved follow-up time is 3 years or more for 20 patients and 5 years or more for 15 patients. The 2 relapses were seen after 6 months and 2¹/ years, respectively

Of the 22 patients remaining in group A or B, 5 have some difficulties at school or in finding work, whereas the rest can attend a normal school or have found work through normal sources with no special help No patient has shown mental deterioration after starting on carbamazepine, provided the seizures have responded to the therapy No side-effects were noted after the first month of therapy

It must be stressed that this material does not represent average epileptic children but a group selected because of difficulties in controlling the seizures with drugs previously available.

REFERENCE

1. Gamstorp, I. A clinical trial of Tegretol in children with severe epilepsy *Develop Med Child Neurol*, *8* 296 1966.

80 NEONATAL SEIZURES EFFECT OF LIDOCAIN

ELISABET NORELL and INGRID GAMSTORP

From the Department of Paediatrics, Central Hospital, Jönköping, Sweden

The material consists of 33 infants (19 boys and 14 girls) below 4 weeks of age, who during the years 1965 to 1970 were admitted to the Department of Paediatrics, Jönköping, because of convulsions. Fits started during the first day of life in 15 patients, during the second day in 7 during the third day in 2, and on the 4th to the 18th day in 9 Neither sex nor age of onset seemed to influence the prognosis.

Signs of asphyxia and/or intracranial bleeding were evident in 20 infants, two of whom also had a low blood sugar Five infants had hypoglycemia (two of these, included in the previous group, also appeared asphyctic). In one patient convulsions started one day after an apparently uncomplicated exchange transfusion performed on the 4th day of life for jaundice of unknown cause. In 9 patients no obvious cause was found.

Twenty three patients (12 asphyctic, 3 hypoglycemic and 8 convulsing for unknown reasons) received phenobarbitol intramuscu larly and/or chloral hydrate by mouth or per rectum, in one case supplemented by dilantin and nitrazepam by mouth. Pyridoxine (100 mg intramuscularly) is considered a diagnostic test and was used in some of the infants, in all of them with no effect on the seizures. All hypoglycemic and several asphyctic infants also had an intravenous glucose infusion, one hypoglycemic infant received pyridoxine and glucose intravenously as the only treatment. Control of convulsions was achieved during the first day of treatment in 6 patients, one of whom

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Sex differences were mainly found in childhood. A statistically significant positive correlation for girls was found with alpha frequency (1—15 years) rhythmic 2.5—4.5 c/sec activity in posterior derivations (2—7 years) and mu rhythm (2—14 years) In the case of boys a statistically significant positive correlation was found with rhythmic 4—5 c/sec activity with posterior accentuation during drowsiness (1—2 years) and rhythmic 6 c/sec activity in anterior derivations also during drowsiness (4—14 years)

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means of the echograms from these points the ventricular size can be estimated either in millimetres or as certain indexes.

In A-scan it is possible to determine from the temporal examination point the third ventricle width, the normal values of which are 2.5—7 mm depending on the patient's age. In estimating the size of the lateral ventricles the brain mantle index is used, in other words, the relationship between the distance of midline echo — end echo and temporal horn echo — end echo (2). Values above 2.4 indicate dilatation of the temporal horns. The lateral ventricle index can also be used. Then the relationship between the common width of the lateral ventricles and the bitemporal diameter of the head is determined (3). Values above 0.30 indicate dilation of the lateral ventricles. With newborns and young infants values up to 0.35 can be received in normal cases.

In B-scan certain landmarks in both coronal and horizontal planes can be visualized. From these landmarks the diameter of the third ventricle can be measured from its various points. In standard coronal plane temporal horns and bodies of the lateral ventricles can be visualized. In the s.c. modified horizontal plane the temporal horns and the frontal horns come into sight. From all these landmarks information as to the size of the lateral ventricles is received. The lateral ventricle index can be counted as in A-scan. On the contrary th end echo in B-scan is impossible to determine so exactly that the brain mantle index could be counted in the same way as in A-scan. The suggestion has been made to count the index from the relationship of the distance between the initial echo and proximal temporal horn echo to the bitemporal diameter of the head (1). But because in the unilateral B-scan the echo of the distal temporal horn is easier to visualize I think it would be more recommendable to count the index from the relationship of the initial echo and the distal temporal horn echo to the bitemporal diameter of the head. When the distal temporal horn echo is used in measuring, the import ance of the variation of the thickness of the skullbone remains less than when the proximal temporal horn echo is used. It is then possible to make comparisons with the A-scan brain mantle index, because it is also counted from the distal temporal horn echo The normal values by the method mentioned above are 0.72—0.76 based on 197 own cases.

In pathological conditions ventricular dilatation is observed for the third ventricle as an enlarged diameter and for the lateral ventricles as a greater than normal lateral ventricle index or brain mantle index counted either according to Schiefer et al. (2) or according to the method presented by me above.

Both the normal brain ventricles and the pathological ventricles and their changes in A-scan and B-scan in different planes are presented as slides. If the lateral ventricles are particularly big, turning the head sideways causes a septum pellucidum deviation influenced by gravity Then a shift of the midline in A-scan to the opposite side of the test point is observed. The changing f the midline shift from one side to the other when turning the head 180 in the case of hydrocephalus is shown by time motion method (Tm)

The advantages of B-scan in determining the size of the ventricles are more reliable identification of landmarks used in measurements, easier exclusion of artificial echoes and the possibility of getting several different landmarks into the same picture. The disadvantages are slight inaccuracy of measurement compared to A-can and more inconvenient performance of the examination when examining a restless patient.

relapsed 2 weeks later In 10 patients the convulsions stopped during the 2nd to 4th day of treatment, whereas 6 patients continued to convulse in spite of the therapy One infant died during convulsions on the third day of life. In this group of 22 surviving children 13 are healthy with a normal psychomotor development at follow up 6 months to 4 years later· convulsions stopped in all of them within 4 days after therapy was started. One child, whose neonatal convulsions stopped on the 5th day has a normal psychomotor development fits relapsed at the age of 9 months, he is now seizure-free on dilantin. One child is mongoloid and thus retarded. The child who relapsed after an initially good response has hydrocephalus and is slightly retarded. All 6 children who continued to have fits after the 5th day are severely retarded and have epilepsy although 2 of them are seizure-free on antiepileptic drugs.

Ten infants (8 asphyctic, 2 of whom also had hypoglycemia, one with convulsions after an exchange transfusion, and one convulsing for unknown reasons) received lidocain in a continuous intravenous glucose infusion through a scalp vein This procedure was preceded in all the infants by a test dose of 100 mg pyridoxine intramuscularly and in 8 also by phenobarbitol and benzodiazepine derivates these measures were ineffective. Two infants received lidocain as the first anticonvulsive drug The initial dose was 4 mg per kg body weight and hour This dose was continued for 1—2 days and then slowly reduced when the seizures were under control. Lidocain was continued for 6—8 days and then followed by phenobarbitol by mouth as a long term treatment. No side-effects were noted. Seizures came under control within 4 days in 8 children and on the 6th day in one child. These 9 children are all seizure-free and 8 show a normal psychomotor development on follow-up at 4 to 18 months of age (one infant is only 2 months old) The 10th child, who had severe hypoglycemia and asphyxia, never became seizure-free and she is severely retarded.

SUMMARY

Of 33 infants with neonatal convulsions 1 died and 23 appear healthy with normal psychomotor development. The duration of fits seems to influence the prognosis, as seizure control was achieved within 4 days in 21 of 23 children doing well whereas in 7 of 9 doing poorly the seizures were never completely controlled (the remaining 2 are a mongoloid child and a hydrocephalic child). Prolonged intravenous infusion of lidocain appears effective in producing control of neonatal seizures and may thus possibly influence the prognosis in the material presented it was used without apparent side-effects.

81 VENTRICLE VISUALIZATION IN TWO-DIMENSIONAL ECHO-ENCEPHALOGRAPHY

T VALKEAKARI

From the Children's Hospital, University of Tu ku, Tu ku, and the Department of Paediatrics Central Hospital, Kokkola, Finland

In ultrasound examination echoes can be received only from surfaces which are more or less perpendicular against the ultrasound beam. For this reason certain examination points in the skull are used in the registration of the size of cerebral ventricles. By

means of the echograms from these points the ventricular size can be estimated either in millimetres or as certain indexes.

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relapsed 2 weeks later In 10 patients the convulsions stopped during the 2nd to 4th day of treatment, whereas 6 patients con tinued to convulse in spite of the therapy One infant died during convulsions on the third day of life. In this group of 22 sur viving children 13 are healthy with a normal psychomotor development at follow up 6 months to 4 years later convulsions stopped in all of them within 4 days after therapy was started. One child whose neonatal convulsions stopped on the 5th day has a normal psychomotor development fits re-lapsed at the age of 9 months, he is now sei zure-free on dilantin. One child is mongoloid and thus retarded. The child who relapsed af ter an initially good response has hydroceph alus and is slightly retarded All 6 children who continued to have fits after the 5th day are severely retarded and have epilepsy although 2 of them are seizure-free on antiepileptic drugs.

Ten infants (6 asphyctic, 2 of whom also had hypoglycemia one with convulsions after an exchange transfusion, and one convulsing for unknown reasons) received lidocain in a continuous intravenous glucose infusion through a scalp vein. This procedure was preceded in all the infants by a test dose of 100 mg pyridoxine intramuscularly and in 8 also by phenobarbitol and benzodiazepine derivates these measures were ineffective Two infants received lidocain as the first anticonvulsive drug The initial dose was 4 mg per kg body weight and hour This dose was continued for 1—2 days and then slowly reduced when the seizures were under control. Lidocain was continued for 6—8 days and then followed by phenobarbitol by mouth as a long term treatment. No side-effects were noted. Seizures came under control within 4 days in 8 children and on the 6th day in one child. These 9 children are all seizure-free and 8 show a normal psychomotor development on follow-up at 4 to 18 months of age (one infant is only 2 months old) The 10th child, who had severe hypoglycemia and asphyxia never became seizure-free and she is severely retarded.

SUMMARY

Of 33 infants with neonatal convulsions 1 died and 23 appear healthy with normal psychomotor development. The duration of fits seems to influence the prognosis, as seizure control was achieved within 4 days in 21 of 23 children doing well whereas in 7 of 9 doing poorly the seizures were never completely controlled (the remaining 2 are a mongoloid child and a hydrocephalic child) Prolonged intravenous infusion of lidocain appears effective in producing control of neonatal seizures and may thus possibly influence the prognosis in the material presented It was used without apparent side-effects.

81 VENTRICLE VISUALIZATION IN TWO-DIMENSIONAL ECHO-ENCEPHALOGRAPHY

T VALKEAKARI

From the Children's Hospital, University of Turku, Tu ku, and the Department of Paediatrics, Central Hospital, Kokkola, Finland

In ultrasound examination echoes can be received only from surfaces which are more or less perpendicular against the ultrasound beam. For this reason certain examination points in the skull are used in the registra tion of the size of cerebral ventricles. By

means of the echograms from these points the ventricular size can be estimated either in millimetres o as certain indexes.

In A-scan it is possible to determine from the temporal examination point the third ventricle width, the normal values of which are 2.5—7 mm depending on the patient's age. In estimating the size of the lateral ventricles the brain mantle index is used, in other words, the relationship between the distance of midline echo — end echo and temporal horn echo — end echo (2). Values above 2.4 indicate dilatation of the temporal horns. The lateral ventricle index can also be used. Then the relationship between the common width of the lateral ventricles and the bitemporal diameter of the head is determined (3) Values above 0.30 indicate dilation of the lateral ventricles With newborns and young infants values up to 0 35 can be received in normal cases.

In B-scan certain landmarks in both coronal and horizontal planes can be visualized. From these landmarks the diamete of the third ventricle can be measured from its various points. In standard coronal plane temporal horns and bodies of the lateral ventricles can be visualized. In the a.c. modified horizontal plane the temporal horns and the frontal horns come into sight From all these landmarks information as to the size f the lateral ventricles is received. The lateral ventricle index can be counted as in A-scan. On the contrary the end echo in B-scan is impossibl to determine so exactly that the brain mantle index could be counted in the same way as in A-scan. The suggestion has been made to count the index from the relationship of the distance between the initial echo and proximal temporal horn echo to the bitemporal diameter of the head (1). But because in the unilateral B-scan the echo of the distal temporal horn is easier to visualize I think it would be more recommendable to count the index from the relationship of the initial echo and the distal temporal horn echo to the bitemporal dia meter of the head. When the distal temporal horn echo is used in measuring, the import ance of the variation of the thickness of the skullbone remains less than when the proximal temporal horn echo is used. It is then possible to make comparisons with the A-scan brain mantle index, because it is also counted from the distal temporal horn echo. The normal values by the method mentioned above are 0 72—0 76 based on 197 own cases.

In pathological conditions ventricular dila tation is observed for the third ventricle as an enlarged diameter and for the lateral ventricles as a greater than normal lateral ventricle index or brain mantle index counted either according to Schiefer et al. (2) or according to the method presented by me above.

Both the normal brain ventricles and the pathological ventricles and their changes in A-scan and B-scan in different planes are presented as slides. If the lateral ventricles are particularly big, turning the head sideways causes a septum pellucidum deviation influenced by gravity Then a shift of the midline in A-scan to the opposite side of the test point is observed. The changing of the midline shift from one side to the other when turning the head 180 in the case of hydrocephalus is shown by time motion method (Tm).

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In pathological conditions ventricular dilatation is observed for the third ventricle as an enlarged diameter and for the lateral ventricles as a greater than normal lateral ventricle index or brain mantle index counted either according to Schiefer et al. (2) or according to the method presented by me above.

Both the normal brain ventricles and the pathological ventricles and their changes in A-scan and B-scan in *different* planes are presented as slides. If the lateral ventricles are *particularly big*, turning the head sideways causes a septum pellucidum deviation influenced by gravity. Then a shift of the midline in A-scan to the opposite side of the *test point* is observed. The changing of the midline shift from one side to the *other* when turning the head 180° in the case of hydrocephalus is shown by time motion *method* (Tm).

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Keywords Echoencephalography hydrocephalus children

82 NEUROLOGICAL ASPECTS OF MENTAL RETARDATION ASSOCIATED WITH CHROMOSOME ABERRATIONS

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Chromosome aberrations in man are known to be frequently associated with mental retardation. This study presents the chromosome aberrations of the patients in the Rin nekoti Institution for the Mentally Retarded Among c. 1300 institutionalized cases 366 patients were selected for karyotyping These patients presented different malformations in association with mental retardation.

Chromosome aberrations were found in 167 cases, of which 98 were males and 69 females. The mean age was 21 1 years (extremes 3—60) The distribution of the level of mental subnormality was mild in 3 cases, moderate in 29 severe in 68 and profound in 67 cases.

Etiologically the patients belonged to three main groups Down s syndrome, the other autosomal aberrations and the sex chromosome aberrations.

In Down s syndrome we found 90 males and 58 females with G+ five translocations (three cases with 46,XY G— t(GqGq)+ one case with 46,XY 14— t(14qGq)+ one case with 46,XX,14— t(14qGq)+ one mosaicism (46,XY/47,XY G+) and one double trisomy (48,XXY G+)

Eight autosomal chromosome aberrations had the karyotypes 46,XX,Bp— (2 cases) 46,XY Bp+ 46,XXCq aberration 46,XY t(Cq—,Dp+) 47,XX,?E+ 46,XX,Er and 46 XX,Gs+

Five sex chromosome aberrations showed 45,X* (2 cases) 45,X/46,XXq— 45,X/46,XXqi/ 47,XXqiXqi* and the already mentioned 48,XXY G+

The mean maternal age of the trisomy mongoloids was high (35 5 years) and that of the translocation mongoloids (29 4) a little higher than in the general population. The distribution curve of maternal ages of the trisomy mongoloids was bimodal, as in generally known from the literature. On the other hand, the maternal age of the other autosomal aber rations was 23 9 years or a little lower than in the general population. Thus it can be concluded that the occurrence of structural autosomal aberrations was not correlated with maternal age. The maternal age of the cases with sex chromosome aberration was 33 5 years.

The mental subnormality was of the same level in the first two groups. The cases with sex chromosome anomaly were not so

deeply retarded as the other groups. However most of the patients in the Rinnekoti Institution have profound retardation.

The size and growth of the patients with chromosome anomaly were markedly smaller than those of the Finnish population in general. The patients with Down's syndrome had a greater tendency to overweight than the others. In particular small head circumference seemed to be correlated with low intelligence level.

The skull in Down's syndrome is flattened in the occipital region. The skull form of the other patients with chromosome anomaly was also remarkably brachycephalic. Consequently this skull form seems to be more usual in these patients than in the general population.

Muscular hypotonia, hypermobile joints and anomalies in the head region were the most frequent findings (60—80 per cent) in the cases with Down's syndrome. Malformations of the extremities and skin were next in frequency (30—50 per cent). Cataract and congenital heart disease were found in rather less than 20 per cent. These have also been the most frequent signs in many other reports. As regards symptoms in these patients, no significant differences occurred between those with a translocation and those with ordinary trisomy.

Among cases with other autosomal aberrations, skin abnormalities and congenital heart disease were frequently seen (60 and 40 per cent). However this group is chromosomally heterogeneous.

All the cases with sex chromosome aberration had gonadal dysgenesis. Other structural anomalies were found only in two cases.

Cerebral palsy and epilepsy were both found in 5 per cent of all mongoloids, as reported elsewhere. Among the G-trisomies the proportion with neurological deficits of supratentorial cerebral origin was lower than among the cases of aberration in other autosomes. On the other hand, nystagmus and muscular hypotonia were more frequent in cases with Down's syndrome. Gas encephalography which was performed on 12 patients with different chromosome aberrations, revealed various forms of cerebral pathology. The patients with some autosomal aberration other than G-trisomy (except 46 XX,Gs+ which probably has no phenotypic effect) had severe cerebral maldevelopment in the supratentorial space as well. Those with Down's syndrome, however had a weakly developed cerebellum and brainstem. Thus it seems as if aberrations in large chromosomes cause a greater disturbance in cerebral development and consequently more neurological deficits than aberrations in small chromosomes.

In this investigation we found chromosomal aberrations in several elder persons, e.g. a 34-year-old female with the Cri-du-Chat syndrome. Thus systematic cytogenetic study of the mentally retarded reveals that some of these patients survive to middle age.

The frequency of mongoloids in the present material was 12.9 per cent and that of other autosomal aberrations 0.6 per cent, both figures agreeing well with those reported from other institutions. The occurrence of sex chromosome aberrations in 0.4 per cent is surprisingly low. The reason for this may possibly be that the mental retardation of these patients is mild and therefore they are not institutionalized.

Cytogenetical diagnoses by Dr A. de la Chapelle. Grants Kehitysvammaliitto r.y. The Sigrid Jusélius Foundation.

83 MINIMAL BRAIN INJURY AND ITS PSYCHOLOGICAL ASPECTS IN CHILDREN WITH RH IMMUNIZATION

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The influence of Rh immunization on the neurological and psychological development of children has been investigated by many authors. They have used clinical neurological methods and psychological development has been measured by intelligence tests (1 2, 3) However the neurological findings have not been compared with results given by multi dimensional and extensive psychological tests The previous works have been mostly restricted to general intelligence tests. The aim of the present work has been to study minor cerebral lesions in Rh immunized children using extensive psychological testing parallel to routine neurological examination.

The material consisted of all Rh-immunized children born in the Turku University Hospital in the years 1958—60 Dead and severely damaged cases had to be excluded. The total number of children examined was 43 Matched pairs of healthy children served as controls. The children were examined at the age of 6—8 years. Clinical neurological examinations and psychological tests were performed. The test patterns were developed by Wuorio (4) Several factors of psychological performance capacity personality and social adaptation were investigated. A statistical analysis of the results was performed using a general purpose computer

The positive neurological findings were few There was significantly more pathology in conjugated eye movements, visual acuity toe-heal walking with open and closed eyes, Romberg test and plantar reflex in the immunized group No severe hearing impairment was noted. The neurological findings correlated significantly to the age of the child at the moment of exchange transfusion, the number of exchange transfusions, the prematurity of delivery bilirubine values (possible correlation) and hemoglobin values (negative correlation)

The psychological examination (for a more detailed report, see 4) confirmed that the immunized children were impaired in their intellectual development. The intelligence defect was greatest in the most severely immunized children. In addition the effects of immunization caused impairment in visual memory visual integration capacity visual motor coordination and fine motor coordination. The psychological tests thus revealed typical signs of organic cerebral damage. Since the neurological findings were scanty it is obvious that minor cerebral damage may remain unnoticed, if the neurological examination is not supplemented with psychological tests. Adequate tests may contribute to the diagnosis of minimal brain injury in a decisive manner with important therapeutic and social consequences.

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84. CRY DETECTOR. A CLINICAL APPARATUS FOR SURVEILLANCE OF PITCH AND ACTIVITY IN THE CRYING OF A NEWBORN INFANT

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Sound spectrographic studies performed on the cry in groups of infants with various diseases have revealed significant deviations from normality in several acoustic characteristics (1, 2, 3). For different reasons, however possibilities for practical application of these results in routine clinical investigation are still limited. the sound spectrographic analysis is expensive, time-consuming and needs specially trained persons both in operation and analysis. This disadvantage increases when there is an evident need of repeating the cry analysis in short intervals.

For the design of a rational pparatus for clinical analysis of the cry we have thus formulated the following conditions

- the price of the apparatus should be within reach of every paediatric unit taking care of newborn infants
- it should make continuous, direct analysis of the cry
- interpretation of the results should be made in the ward by personnel without special education.

According to the experience of paediatricians and the results of spectrographic analyses of the cry there is one cry characteristic which dominates in the abnormal cry namely an elevation in its fundamental frequency (pitch) In addition, abnormal cry activity of the infant, i.e. a low or high number of cry signals during a certain period of time, is often an obvious sign of abnormality to the paediatrician. We have thus selected these two cry characteristics — pitch and quantity of crying — to be used as signal material for direct detection in a first attempt to construct a cry analyzer for everyday clinical purposes.

Technical specifications of the first laboratory model of *Cry detector* reported in this paper

1. Acoustical signal longer than 400 ms is considered as a cry and registered with a delay of 5 sec.

2. The present detector uses two channels. The first channel detects intensity above pre-set threshold in the frequency range of 150—7000 Hz. This is called the *total channel* and counts all the cry signals with a duration of more than 400 ms The second channel detects cry signals in the same way but within a limited frequency range, running from 1000 to 7000 Hz. This channel is supposed to detect cry signals with an *abnormally high pitch*.

3. Each channel is supplied with an event counter and also a device *for* collecting cry material on tape for eventual further spectrographic analysis.

For further development of the *Cry detector* the frequency range is quantized in 3 channels for improving the possibility of classifying the degree of deviation in pitch. This model is under construction. To obtain the best technical and economical solution, different approaches to pitch analysis of the cry are taken into consideration and simulated on the *STL* computer (KTH).

The cry material analyzed (Fig. 1.) consists of continuous registration of spontaneous crying from 15 normal and 2 pathological newborn infants during 24 hours between the first and fifth days of life. The data were recorded from the counters every 60 minutes.

Clinical reports from the cases

Case 1 Normal number of chromosomes but structural abnormality in one of the chromosomes in group D No abnormal clinical or neurological findings during the newborn period.

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immigrants — in recent years about 17 per cent — are children. These constitute a sizeable proportion of the children seen at child welfare centres.

A study of immigrant children has been carried out in the district of Upplands Vasby 25 kilometers from Stockholm. In this district 16 per cent of all children are immigrants. Of preschool immigrant children 94 per cent were registered at the child welfare centre, compared with 98 per cent of Swedish children of the same ages. The frequency of visits to the welfare centre was significantly lower in the case of children whose parents did not speak Swedish, compared not only with Swedish children but also with other immigrant children. Consequently the immigrant children were not so well vaccinated as the Swedish children. The frequency of caries was calculated by a dentist at the child welfare centre. In a screening of children 1—7 years of age, performed with simple means, he found that Swedish children were caries-free in 59 per cent of cases but immigrant children in only 24 per cent. Records from the dental care centre in the district also showed that the immigrant children had significantly more DMF (Decayed, Missing, Filled) — teeth than the Swedish children.

Ignorance of language is the most important problem in the health care of immigrant families. It is also necessary to give immigrants thorough information on health matters. Our knowledge of immigrants must be widened. For this purpose, a prospective medico-social survey of immigrant families in some districts north of Stockholm has begun. The team performing the study consists of a dentist, a nurse, and the author a paediatrician. The work emanates from the Medico-social Institution at Uppsala University.

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86. INFLUENCE OF SOME BIRTH ABNORMALITIES ON THE PSYCHOLOGICAL DEVELOPMENT OF THE CHILD

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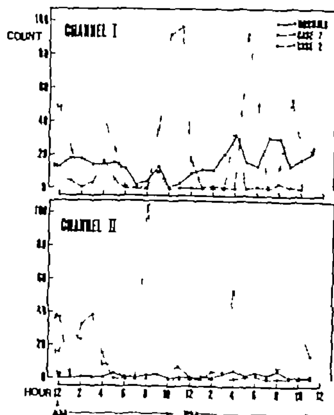


Fig 1 Hourly counts of signals in channel I (reduced by signals in channel II) and in channel II in 15 normal and 2 pathological newborn infants during 24 hours between the first and fifth days of life

Case 2. Tremor irritability and hypertonia from the first day of life. Clinical diagnosis hyperexcitability syndrome.

The total number of signals during the 24 hours in the 15 normal cases averaged 384 the average for channel I (reduced by signals in channel II) being 351 and 33 for channel II. Respective values for case 1 were 349 and 270 for case 2 445 and 263

Applications of the *Cry detector* in clinical work and cry studies

surveillance and diagnostic help

— of newborn infants with different diseases affecting the central nervous system or respiratory system

— of premature infants

— of infants with feeding problems

adaptation of the infant to different feeding scheludes.

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Key words Cry detector surveillance of crying, newborn infant.

85 IMMIGRANT CHILDREN AT A SWEDISH CHILD WELFARE CENTRE

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In the last decade Sweden has been a country of immigrants. Every year 30 000—50 000 foreigners come to settle in Sweden, and today about 360 000 foreigners live here. Most of these are Scandinavians, particularly Finns, who form 30—40 per cent of all immi grants, Southern Europeans making up 15—20 per cent. An increasing proportion of the

Our results agree with a study by *Albers et al.* (1966) who, in 131 newborns of healthy mothers, found all blood cultures from the umbilical vein negative when blood culture was made immediately after birth. They disagree with a study by *Pryles et al.* (1963) who found 41 per cent positive blood cultures in 358 newborns when made from umbilical cord blood immediately after birth.

In the study by *Albers*, 0 7 per cent developed bacteriologically proved septicemia and in the study by *Pryles et al.* 5 per cent. In our material probably 2.7 per cent has suffered from bacteriologically proved septicemia.

Table 3 *Blood culture and clinical course.*

Blood culture	Alive	Died +S	Died −S
Negative	129	2	3
Positive			
Umbilical	4	0	0
Peripherical	6	0	0

S = Septicemia t autopsy

88. BACTERIEMIA IN NEWBORNS AFTER CATHETERIZATION OF THE UMBILICAL VEIN

O PETTAY E. ANDERSIN and J ELFVING

From the Children' Hospital, University of Helsinki, Helsinki, Finland

Catheterization of the umbilical vessels is a common procedure in neonatological wards, and, at least theoretically it is associated with some risk of infection. At the Children s Hospital in Helsinki we have made blood cultures in connection with exchange transfusions. Cultures were made both through the catheter and from a peripheral vein. The frequency of positive cultures increased with increasing age of the child at the time of the exchange transfusion. The most frequent bacteria found were E. coli, Enterococcus, and Staph albus, i.e. the normal colonizers of the umbilicus. Proteus, Pseudomonas, and Klebsiella were also quite common. Clinical signs of infection were very rare. We have usually given antibiotics prophylactically to these children, but have recently initiated a study to determine the value of such prophylaxis.

89 INFECTION OF NEWBORN INFANTS WITH STREPTOCOCCUS AGALACTIAE (LANCEFIELD GROUP B) IN RELATION TO ITS OCCURRENCE IN THE VAGINAL FLORA OF TERM PREGNANT WOMEN

G BERGQVIST B. HURVELL, E. THAL and VLASTA VACLAVINCOVA

From the Paediatric Clinic, St. Görans Hospital, National Veterinary Institute & Gynaecologic-Obstetric Clinic, Sabbatsbergs Hospital, Stockholm, Sweden

Since the end of the 19th century the relation between bovine mastitis and streptococci has been well known. These bacteria are called Streptococcus agalactiae and belong to Lancefield group B Earlier they were considered saprophytic in man, but in the

SESSION A III

NEONATAL INFECTIONS

CHAIRMEN TORBEN IVERSEN and PETER JOHAN MOE

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87 BACTERIEMIA DURING THE FIRST DAY OF LIFE

C. J INGOMAR

From the University Clinic of Paediatrics Rigshospitalet, Copenhagen, Denmark

During the year 1969 a blood culture was made from 144 newborn infants admitted to the department of neonatal diseases, Rigshospitalet, Copenhagen. Blood was drawn from a peripherical vein or from the umbilical vein within the first day of life and before any antibiotics had been given.

As no kind of surgery had been performed and as no kind of catheters had been inserted, a positive blood culture was supposed to be a sign of primary septicemia

Of the blood cultures 93 per cent were negative 5 per cent showed growth of Stafylococcus albus and 2 per cent showed growth of other bacterias. Table 1

No relation was found between the result of blood culture and problems of pregnancy usually associated with primary septicemia Table 2.

The occurrence of Stafylococcus albus seems to be a result of contamination, as 1) the occurrence could not be related to the clinical condition, 2) none of the infants died, in spite of either lack of treatment or treatment with kanamycin to which stafylococcus was insensitive.

Two infants died from septicemia associated with meningitis, as demonstrated by autopsy and caused by Klebsiella pneumoniæ. Blood culture from a peripherical vein had been negative on the first day of life. In 2 cases septicemia (streptococcus fæcalis 1 Klebsiella pneumoniæ 1) possibly was the cause of symptoms. Table 3

Table 1 *Result of blood culture on the first day of life*

	Number	Negative	Positive Staph. alb	Positive other bact.
Peripheral blood	93	87	6	0
Umbilical venous blood	51	47	2	2

Table 2. *Clinical factors and result of blood culture*

	C	S	Number	Negative	Staph alb	Other bact.
I	+	+	26	25	1	0
II	+	—	27	24	3	0
III	—	+	24	19	3	2
IV	—	—	67	66	1	0

C = Complications of pregnancy S = symptoms of septicemia.

I = complicated pregnancy and symptoms, II = complicated pregnancy but no symptoms, III = normal pregnancy and symptoms, IV = normal pregnancy but no symptoms.

Our results agree with a study by *Albers* et al. (1966) who, in 131 newborns of healthy mothers, found all blood cultures from the umbilical vein negative when blood culture was made immediately after birth. They disagree with a study by Pryles et al. (1963) who found 41 per cent positive blood cultures in 103 newborns when made from umbilical cord blood immediately after birth.

In the study by *Albers*, 0.7 per cent developed bacteriologically proved septicemia and in the study by *Pryles et al.* 5 per cent. In our material probably 2.7 per cent has suffered from bacteriologically proved septicemia.

Table 3 *Blood culture and clinical course.*

Blood culture	Alive	Died +S	Died −S
Negative	129	2	3
Positive			
Umbilical	4	0	0
Peripherical	6	0	0

S = Septicemia † autopsy

58 BACTERIEMIA IN NEWBORNS AFTER CATHETERIZATION OF THE UMBILICAL VEIN

O. PETTAY, K. ANDERSIN and J. ELFVING

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infected. In the previously published cases (1) maternal obstetrical complications were common and this could be one of the reasons for the high frequency of severe infections among these newborn infants.

The question whether these bacteria are more likely to cause neonatal infections than other pathogenic bacteria is debatable. This investigation, however does not confirm the high risk hypothesis, but the risk for the infants seems to be increased compared with those born by non-vaginal carriers.

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90. THE ROLE OF INFECTION AND ANOXIA IN KERNICTERUS

INGE TYGSTRUP and B. FRIIS-HANSEN

From the University Clinic of Paediatrics Rigshospitalet, Copenhagen, Denmark

During the past four years 24 cases of kernicterus were observed among 325 autopsies of infants of low birth weight. The diagnosis was established by macroscopic examination of the formalin-fixed central nervous system. Varying intensities of yellow staining were observed.

In 143 cases a bacteriological examination was performed at the post mortem, and a significant bacterial growth was found in 53 cases. Of these, 13 had kernicterus but except for pneumonia no signs of widespread infection were found by microscopic examination of the organs. In 6 cases with manifest meningitis at death only 3 cases of kernicterus were seen.

The role of anoxia and the concentration of serum bilirubin and of the bilirubin binding capacity of the serum-albumin as factors in the development of kernicterus will be discussed briefly. Nearly all the cases with kernicterus, both with and without bacterial growth, showed in microscopy widespread degenerative changes in the central nervous system most probably caused by anoxia.

These findings suggest that bacterial spread takes place shortly before death, often superimposed upon anoxia.

91 TRANSPLACENTAL PASSAGE OF AZIDOCILLIN AMPICILLIN AND PENICILLIN G DURING EARLY AND LATE PREGNANCY

O WASZ-HÖCKERT, S. NUMMI, SALME VUOPALA and P A. JÄRVINEN

From the Department of Paediatrics, University of Oulu, Oulu, Finland

The levels of azidocillin, ampicillin and penicillin G in maternal serum, fetal serum and amniotic fluid after oral or intramuscular administration were studied in 169 pregnant women during the first trimester in connection with legal abortion and in 398 women

last decades an increasing number of infec tions with these organisms have been report ed among both adults and newborn infants. In adults they cause wound infections, osteomyelitis, endocarditis and puerperal and uri nary tract infections.

In newborn infants septicemia, meningitis and omphalitis, caused by B Streptococci, have been reported (2, 3)

Hood et al. (2) found B Streptococci in vaginal flora in 5—10 of healthy pregnant women. The same authors also reported that severe infection among infants was common if the mothers had B Streptococci in vagina. During the last few years several cases of neonatal infections have occurred in the Stockholm area and 5 of these cases have already been reported (1) In four of these five cases the same organism was isolated from the mothers genital tracts.

Because of these facts we started this investigation to estimate the frequency of B Streptococci in vagina in term pregnant women and to evaluate the risk for the newborn

MATERIAL AND METHODS

From 118 consecutive pregnant women visiting the motherhood advisory clinic from November 1969 to April 1970 clinical specimens (genital tract) were taken about 1 month before expected delivery

These specimens from urethra and vagina were examined for B Streptococci. If a woman had these bacteria in her genital tract new specimens (throat and vagina) were taken in connection with the delivery

Umbilical cord blood specimens were taken for bacteriological examination and the child was placed in a special nursery for close observation on infections. Cultures were also taken from throat, blood, urine and in some cases faeces the first two days after birth. All specimens were sent for bacteriological examination both to a routine laboratory and to the National Veterinary Institute, where the isolations of B Streptococci were performed. The identification was based on the macroscopic morphology sodium hippurate test, CAMP test and the precipitin test with group specific antiserum. Other clinical tests were micro-erythrocyte sedimentation rate, white blood count, immune electrophoresis (cord blood) microscopic urine studies and pulmonary X ray

RESULTS

In 17 of the 118 women examined one month before delivery group B Streptococci were cultured from their genital tract (17 urethra and 11 also in cervix) In connection with delivery 3 of 17 had positive isolation from throat and 4 from the genital tract. Until now new cultures have been taken 2—4 months post partum from 2 women and both still had streptococci in their genital tract.

Of the children only one had clinical signs of infection omphalitis (Streptococcus group B) All throat cultures were negative In 4 cases umbilical cord blood was positive but subsequent blood cultures were negative. From fifteen children urine cultures were performed and one was positive, but the subsequent cultures were negative Nine faeces cultures were taken of which one was positive. Laboratory routine tests (blood, urine) and pulmonary X ray were normal in all cases.

DISCUSSION

This investigation shows that B Streptococci are common among pregnant women, as has been shown in other parts of the world (2 3). The main reservoir seems to be the female genital tract. The frequency of positive throat cultures was rather low The risk for the infant of being infected seems to be in accordance with other authors opinions (2) Like them we found cases with positive cord blood where infection did not develop. This finding is contradictory to the opinion of Hood et al (3) It is of interest to note that of 11 previous positive mothers 7 had negative cultures at delivery In none of the deliveries did obstetrical complications occur We know that complications such as a long time between rupture of membranes and delivery *ablatio placentae* elevated temperature in the mother increase the risk of the infant being

infected. In the previously published cases (1) maternal obstetrical complications were common and this could be one of the reasons for the high frequency of severe infections among these newborn infants.

The question whether these bacteria are more likely to cause neonatal infections than other pathogenic bacteria is debatable. This investigation, however does not confirm the high risk hypothesis, but the risk for the infants seems to be increased compared with those born by non-vaginal carriers.

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92. CEPHALOTHIN IN NEONATAL INFECTIONS

T HALLBERG and N W SVENNINGSEN

From the Department of Medical Microbiology and Paediatrics University of Lund Lund, Sweden

259 cases of neonatal infections were treated with CEPHALOTHIN (Keflin®) at the Neonatal Unit, Department of Paediatrics in Lund during a 3 year period 1967—1970 (Table 1) Part of this material has been presented earlier (1) Cephalothin was administered in a dosage of 40—80 mg/kg/day in 2—3 i.m. injections or in continuous i.v infusions. In 212 cases no additional antibiotics were needed whereas 16 infants received carbenicillin and 31 infants ampicillin, kanamycin, streptomycin or cloxacillin as well

Sodium cephalothin a cephalosporine derivative has antibacterial activity against both gram positive and gram negative organisms. Exceptions are enterococci most strains requiring cephalothin serum levels of 10 μg/ml or more to be inhibited, and Pseudomonas aeruginosa which is resistant to cephalothin (2)

Complete recovery on cephalothin treatment was achieved in 212 infants. Among 41 patients with septicaemia and/or meningitis 17 cases recovered on cephalothin treatment, whereas 10 infants were successfully treated with a combined therapy of cephalothin and carbenicillin. In the last group 3 cases of Pseudomonas septicaemia were included. The remaining 14 cases of septicaemia and/or meningitis required other antibiotic drugs, but 7 infants died.

In 39 cases of urinary infections urine cultures obtained before treatment identified the etiologic bacteria as Pseudomonas aeruginosa, resistant to cephalothin, in 3 cases. In 36 patients E. coli, enterococci or Proteus mirabilis, all sensitive to cephalothin, were isolated. At repeated urine culture after cephalothin treatment for 10 days, strains resistant to cephalothin emerged in 4 cases, whereas the urine became sterile in the remaining 32 patients.

During and after treatment with cephalothin laboratory examinations including BUN GOT and GPT were within normal range. Drug induced leucopenia or thrombocytopenia was not observed. In 2 infants the direct Coombs test was positive without evidence of hemolytic disease In 2 cases a local abscess at the injection site occurred. At serum levels of cephalothin of 30—40 μg/ml the reserve-binding capacity of serum albumin, measured with the HBABA index method, was only slightly decreased

In about 40 cases blood specimens were obtained at various intervals for assay of cephalothin after intramuscular or during continuous intravenous administration. The assays were made by a modification of the agar well diffusion method requiring only 20 μl of serum for a single determination. All tests were run in duplicate During continuous i.v administration of 40 mg/kg/day the cephalothin serum levels were 7—22 μg/ml in fullterm infants and 24—35 μg/ml in preterm low birth weight infants, while at i.v infusion

Table I. Clinical diagnosis number of infants, average duration and results of treatment with cephalothin as the initial antibiotic agent in neonatal infections.

Clinical diagnosis	No. of infants Total	F	P	Average duration of treatment (days)	Results +	(+)	—
Respiratory inf.	97	50	47	14	86	7	4
Urinary inf.	39	18	21	10	32	6	1
Cutaneous inf.	8	5	3	7	8	0	0
Septicaemia	31	13	18	19	15	13	3
Meningitis	10	4	6	20	2	4	4
Premature rupture of membranes (24 hours)	48	21	27	7	47	1	0
Bacteraemia t umbil. vessel catheterization	26	12	14	9	22	4	0
Total N	259	125	134		212 (82 %)	35 (14 %)	12 (4 %)

Abbreviations F = Fullterm infants.
P = Preterm low birth weight infants.
+ = Responding to cephalothin treatment.
(+) = Not responding to cephalothin, but requiring additional antibiotic agents.
— = Dead in neonatal infections.

of 60 mg/kg/day serum levels of 32—41 μg/ml and 32—52 μg/ml respectively were obtained On these dosages no accumulation of cephalothin occurred, not even in preterm low birth weight infants. When 80 mg/kg/day was administered cephalothin serum levels of 32—50 g/ml in fullterm infants and 50—120 μg/ml in preterm low birth weight infants were found, but no side-effects were observed

According to our studies the dosage of cephalothin in order to obtain lasting serum levels of 30—40 μg/ml during continuous i.v administration should be 40—60 mg/kg/day for preterm infants and 60—80 mg/kg/day for fullterm infants. Being without any significant side-effects, cephalothin is a valuable alternative drug to more toxic antibiotic agents in the management of neonatal infections.

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From the Paediatric Department and Department of Bacteriology Karolinska Sjukhuset, Stockholm, Sweden

There is an obvious risk of accumulation of aminoglycoside antibiotics in treatment during the first week of life, when renal excretion is slow Simple measures for control of plasma concentration of these drugs are therefore needed. We have adapted the paper

with termination of pregnancy Samples for penicillin assay were obtained 1—20 hours after the administration. *In the maternal* serum peak levels of all 3 penicillins were found 1—2 hours after the administration of the penicillins. It was found that penicillin compounds were transferred to the fetus and the amniotic fluid reaching therapeutic levels except in the amniotic fluid in the first trimester

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MENTAL RETARDATION

CHAIRMAN BENGT HAGBERG

94. HISTOPATHOLOGICAL DIAGNOSIS OF PROGRESSIVE INFANTILE AND JUVENILE ENCEPHALOPATHIES WITH MENTAL RETARDATION

P SOURANDER

From the Department of Pathology, Sahlgrenska Sjukhuset, U iversity of Gothenburg Gothenburg, Sweden

Mental retardation i.e. retardation of highest level nervous activities, may be one of the most prominent and frequently one of the earliest symptoms in various kinds of progressive diseases affecting the nervous system in infancy childhood and adolescence.

While many of these diseases e.g the sphingolipidoses, represent genetically determined metabolic disorders of a more or less generalized character others e.g. subacute sclerosing panencephalitis, are of infectious origin. An additional disease group includes various degenerative processes of obscure etiology and pathogeneses, e g progressive myoclonus epilepsy

Since differential diagnosis between the three principal nosological categories of cases is of primary importance for future family planning and medical care, there is an urgent need f r recognition, already during life, of the true character of the disorders.

This report is a short review and evaluation f current histological and histochemical methods used for biopsy and autopsy diagnosis and of the results obtained when such methods were applied to differentiate between progressive encephalopathies with mental retardation.

Particular attention was paid to maladies recognized in the Scandinavian countries. An essential part of the author's and his collarobators' personal experience is documented in the papers included in the reference list.

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disc bioassay technique for analysis of streptomycin levels and evaluated its usefulness for routine control of treatment in newborn infants. The method has been shown to be reliable even in the presence of penicillinase-stabile penicillins. The amount of plasma needed for each analysis is only 10 μl. Capillary blood is used, which allows repeated sampling with short intervals. This is necessary for investigation of the pharmacokinetic parameters in the individual patient. The method has been used for analysis of the interindividual variation in distribution volume and plasma half life.

MENTAL RETARDATION

CHAIRMAN BENGT HAGBERG

94. HISTOPATHOLOGICAL DIAGNOSIS OF PROGRESSIVE INFANTILE AND JUVENILE ENCEPHALOPATHIES WITH MENTAL RETARDATION

P SOURANDER

From the Department of Pathology, Sahlgrenska Sjukhuset, University of Gothenburg Gothenburg, Sweden

Mental retardation i.e. retardation of highest level nervous activities, may be one of the most prominent and frequently one of the earliest symptoms in various kinds of progressive diseases affecting the nervous system in infancy childhood and adolescence.

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95 THE BIOCHEMICAL APPLICATION OF SKIN BIOPSIES FOR THE CLINICAL DIAGNOSIS OF LYSOSOMAL ENCEPHALOPATHIES

J CLAUSEN and J C. MELCHIOR

From the Neurochemical Institute Copenhagen and the University Clinic of Paediatrics Rigshospitalet, Copenhagen, Denmark

The specific enzymic activity of six lysosomal enzymes (α-mannosidase β-galactosaminidase, β-galactosidase, α-fucosidase, sulphatase A and acid phosphatase) was determined in skin biopsies and in leucocytes. The lysosomal enzymic activity of normal individ

mals of different age groups was correlated with that of patients with clinical signs of progressive encephalopathies.

Although only a few cases showed absolute lack of one of the enzymes assayed, a significantly lowered activity of enzymes involved in the degradation of glycolipids and acid mucopolysaccharides was found in entities showing similarities with syndromes related to gangliosidosis (e g Tay-Sach s disease) sulfatide lipidosis, and mucopolysaccharidosis. Significantly lowered activities were however also encountered in syndromes not strictly classifiable

The findings are compared to the clinical picture, the radiological findings and the biochemical alterations in urine and blood.

96 SOME AUTOSOMAL ABERRATIONS ASSOCIATED WITH MENTAL RETARDATION

K.-H. GUSTAVSON

From the Department of Paediatrics, University Hospital, Uppsala, Sweden

The following chromosomal aberrations are described.

Chromosome No. 4 short arm deletion syndrome characterized by ocular hypertelorism, prominent glabella, low set simple ear with preauricular dimple, cleft lip and palate or midline scalp defects, severe growth, motor and mental retardation.

Chromosome No. 13 long arm deletion syndrome characterized by microcephaly trigonocephaly micrognathia, large malformed ears, hypertelorism, microphthalmus, hypoplastic or absent thumbs and imperforated anus.

Chromosome No 18, long arm deletion syndrome characterized by midfacial hypoplasia, atretic r narrow ear canal with hypertrophied antihelix, high frequency of whore digital pattern, mental and growth deficiency

Chromosome No 13 partial trisomy syndrome in 4 children, is presented. It is characterized by severe retardation in growth and development, underdeveloped musculature with hypotonia, microcephaly micrognathia, large malformed ears, preauricular papillomas, cleft palate, long slender hyperflexible fingers stereotypic rhythmic movements of the hands.

A congenital malformation syndrome including agenesis of the corpus callosum, mental retardation, muscular stiffness, articular extension defects, long and slender trunk, vertebral anomalies and deep palmar and plantar furrows is presented. The syndrome is associated with mosaic trisomy of an autosome in the 6—12 group.

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The specific enzymic activity of six lysosomal enzymes (α-mannosidase β-galactosaminidase β-galactosidase α-fucosidase, sulphatase A and acid phosphatase) was determined in skin biopsies and in leucocytes. The lysosomal enzymic activity of normal individ

an enlarged 4th ventricle, combined in a few cases with a small brainstem, was found. In cutis verticis gyrata and the mental retardation syndrome a hypoplastic cerebellum, cerebellar atrophy or a narrow posterior fossa combined with varying types and degrees of supratentorial macro- or microventriculy were observed. It could be concluded that most and probably all cases of cutis verticis gyrata and the mental retardation syndrome exhibit maldevelopment of the skull and/or brain.

In all, slightly over 90 per cent of the GEG findings of patients with profound mental retardation were pathological. In a number of cases the aetiological diagnosis was changed in the light of these results, aetiology of prenatal origin increasing and that of primary birth injury diminishing considerably. Probably an anomalous brain or one that is prenatally impaired in some other way does not sustain birth as well as a healthy brain does. In those cases in which GEG revealed nothing definitely pathological, the cerebral lesion may be on the microscopic level (e.g. mild dysplasia) or these cases may simply present the part that corresponds to low I.Q.s in the Gaussian curve of intelligence distribution in the general population.

The use of the fractional GEG technique is one reason why the results of this study have been more revealing than those of some earlier studies on the same subject. GEG per se and especially combined with certain other neuroradiological methods in accordance with the known indications seems to afford valuable information on the cerebral lesion of even profoundly mentally retarded patients. This agrees well with experiences with series of children (e.g. 1).

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98. NEW CLINICAL ENTITIES WITHIN THE CONCEPT OF AMAUROTIC IDIOCY

B. HAGBERG

From the Department of Paediatrics, University Hospital, Uppsala, Sweden

97 GAS ENCEPHALOGRAPHIC FINDINGS IN PATIENTS WITH PROFOUND MENTAL RETARDATION

M. IIVANAINEN

From the Department of Neurology University of Helsinki, Helsinki, and Research Department, Rinnekoti Institution for the Mentally Retarded, Majalampi, Finland

Medical science has shown mainly on the basis of autopsy findings that mental retardation is a symptom of cerebral origin. Consequently if we investigate the brains of mentally retarded persons, we are in fact investigating the aetiology of mental retardation. Some methods, e.g gas encephalography (GEG) make investigation possible during early life when the possibilities for treatment and rehabilitation may be better than later

As part of a larger study to be published separately GEG was done on 197 patients with profound mental retardation (I Q below 20) in the hope of throwing further light on the aetiology of mental retardation. The ages of these patients at the time of GEG were 0—5 years in 8 cases, 6—10 in 37 11—15 in 47 16—20 in 37 21—25 in 36 26—30 in 24 and over 30 years in 8 cases. There were 113 males and 84 females

Epilepsy was found in 130 cases, extremital paresis in 105 dyskinesias in 54 psychotic signs in 14 and ataxia in 11 cases. Ataxia could not be excluded in 40 cases because of severe paresis.

The electroencephalogram was pathological in 95 per cent and focal discharges were noted in 35 per cent of the cases studied.

Fractional GEG was performed under general anaesthesia according to the known indications and contraindications. The main findings were symmetric macroventriculy in 53 cases, asymmetric macroventriculy in 25 hemimacroventriculy in 25 enlargement of temporal horns in 17 other local ventricular deformity in 5 cortical lesion in 7 cerebellar lesion in 14 anomaly in 25 miscellaneous abnormalities in 5 no intraventricular gas filling in 3 and nothing definitely pathological in 18 cases.

Several combinations of encephalographic findings of infratentorial and supratentorial central and cortical regions were observed. The ventricular size varied from microventriculy to severe macroventriculy but most patients had large ventricles. Agenesis of septum pellucidum was found in 5 cases, a cavity in the septum pellucidum in 4 a broad septum pellucidum in 3 agenesis of the corpus callosum in 3 and cupular corpus callosum in 9 cases. Cortical lesions were found in 37 cases, but in 114 cases the cortical gas filling was not sufficient for interpretation. Altogether 81 cases exhibited some sort of infratentorial abnormality

The GEG findings were not specific, but in several disorders they were somewhat typical and often pathognomonic. A case with the sequelae of subdural haematoma was diagnosed 19 years after the primary head trauma which occurred in early childhood. In all the cases associated with different chromosome aberrations various sorts of cerebral maldevelopment were detected. On the other hand, the great majority of cerebral malformations were not associated with chromosome aberrations. Such malformations included different forms of single lateral ventricle in connection with which some other pathological condition was also visible in the encephalogram at the same time. The most usual finding in psychotic patients was enlargement of the temporal horns, especially the left one, thus suggesting a temporal lesion. In cases with chronic phenytoin intoxication,

an enlarged 4th ventricle, combined in a few cases with a small brainstem, was found. In cutis verticis gyrata and the mental retardation syndrome a hypoplastic cerebellum, cerebellar atrophy or a narrow posterior fossa combined with varying types and degrees of supratentorial macro- or microventricuIy were observed. It could be concluded that most and probably all cases of cutis verticis gyrata and the mental retardation syndrome exhibit maldevelopment of the skull and/or brain.

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100 TREATMENT OF JUVENILE RHEUMATOID ARTHRITIS BY ANTIMALARIAL DRUGS

Dosage in Syrup and Tablets

ANNA LIISA LAAKSONEN J. E. SUNELL and K. JUVA

From the Children's Hospital and the Department of Clinical Chemistry, University Hospital, Turku, Finland

Treatment of juvenile rheumatoid arthritis by antimalarial drugs (chloroquine phosphate and hydroxychloroquine sulphate) causes difficulties because tablets now available are meant for adults and are thus too strong for children.

It is often difficult to divide the tablets. The alternative is to administer the drug every other or every third day but this causes great changes in the serum concentrations, and high concentrations often cause anorexia and nausea.

By using chloroquine phosphate or hydroxychloroquine sulphate as syrup, great changes in the serum concentration are avoided. Furthermore, it is easy to calculate the dosage individually with regard to the child's weight and surface area. To the smallest children (e.g. 10 months — 3 years) it is more convenient to administer syrup than crushed tablets.

Absorption of syrup was followed in the present investigation by determining the daily serum concentration at the beginning and during the course of treatment. The achieved serum concentrations correspond to those of patients treated with tablets, if the drug is administered daily. During syrup medication, no more complications were observed than with tablets if the dosages per kilo of body weight and surface area are identical. It is emphasized that the daily dose of chloroquine phosphate must not exceed 5 mg/kg. The daily dose of hydroxychloroquine sulphate can be elevated up to 8—10 mg/kg without the complication frequency clearly rising. Ceratopathy is considered a sign of overdosage because it is simultaneously accompanied by other side effects, such as anorexia, light sensitivity, loss of hair etc. Interruption of antimalarial medication or decrease in dosage eliminated the complications noted in the present investigation.

Determination of serum concentration of antimalarial drugs is considered to be a clinically important investigation, because it is a way to observe in advance too high serum concentrations, making it possible to diminish the dosage before the complications appear. It is particularly important to follow the function test of the liver at regular intervals during the medication. A clear connection has been noted between unexpectedly high antimalarial serum concentrations and liver lesions: e.g. GOT and GPT have been elevated.

The number of *complications* is increased if the treatment is started with a dosage two or three times greater than normal. In addition, it elevates the serum concentration above the therapeutic level, and in as little as three weeks distinct ceratopathy is noted to develop.

It is advizable to follow the ECG before and during antimalarial medication, because this medication may cause changes in the ECG: a fall in the ST interval and spreading of the QRS complex, which can lead to a fallacious diagnosis of carditis.

SESSION C III

RHEUMATOLOGY

CHAIRMAN HELENA SVANTESSON

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99 EXTRA ARTICULAR MANIFESTATIONS IN JUVENILE RHEUMATOID ARTHRITIS

Diagnostic Difficulties

HELENA SVANTESSON and S. GARWICZ

From the Paediatric Unit of the Department of Rheumatology University Hospital of Lund, Lund, Sweden

The authors present 120 cases of juvenile rheumatoid arthritis seen in the child rheumatology unit, Lund which serves as a centre for treatment of juvenile rheumatoid arthritis for the whole of Sweden. In 20 % the disease started with septic fever without articular manifestations. In half of these cases a pericarditis was diagnosed. Other early signs were leucocytosis, hepato-splenomegaly and a temporary rash. Usually these cases were thought to have sepsis, leucemia, rheumatic fever or meningitis (because of pain and stiffness in the neck).

Among later extra-articular manifestations were uveitis in 15 %. 4 % developed a cataract, half of these probably due to steroid treatment in large doses. In 7 % there was a nephrotic syndrome due to kidney amyloidosis. In these cases proteinuria developed between 4—7 years after the onset of the disease. There was no evidence for the hypothesis that amyloidosis is more common in steroid treated cases.

Neurologic signs may appear because of medullary compression consequent to a subluxation of atlas in relation to dens epistrophei.

In one case there was laryngeal stridor and hoarseness, and the respiratory tract was obstructed because of noduli below the glottis.

Articular manifestations may also cause diagnostic difficulties. This is especially true of monarthritis, which is often assessed as growing pains traumatic conditions, osteomyelitis and in earlier days as tuberculous arthritis. Serologic tests are of little aid, since only about 10—15 % of the children with juvenile rheumatoid arthritis show a positive Waaler Rose test, this mainly among older children.

To demonstrate the diagnostic difficulties in juvenile rheumatoid arthritis the authors relate the initial diagnosis of 50 children, who were later referred to our clinic.

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It is advizable to follow the ECG before and during antimalarial medication, because this medication may cause changes in the ECG a fall in the ST interval and spreading of the QRS complex, which can lead to a fallacious diagnosis of carditis.

101 SOME ASPECTS OF THE EVALUATION OF LOCAL RHEUMATOID ACTIVITY

P TISELIUS

From the Regional Hospital, Örebro, Sweden

Interest has been focused on one of three *common manifestations* of the disease, viz. joint heat. Infrared thermography and its application in the assessment of joint temperatures in R. A. is described. Special attention is given to quantitation of the thermogram, a problem that must be taken into account if the method is to be used in the routine work of clinical rheumatology. The importance of standardized measuring conditions is stressed. Quantitative methods based upon the use of isotherms and an infrared radiation reference source are suggested.

In order to illustrate the use of thermal scanning in clinical practice this has been applied in studying joint temperature as a measure of local inflammatory activity produced by the adoption of some common principles of antirheumatic treatment. Further studies have also shown that unidirectional changes occur in heat emission from active joints and laboratory measurements of joint activity i.e. white blood cell count and lactic dehydrogenase isoenzyme content in synovial fluid. This nontouchable method appears to be of value in grading local joint rheumatoid activity in children as well as in adults.

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102. ADRENOCORTICAL FUNCTION IN CHILDREN WITH RHEUMATOID ARTHRITIS

J MULDER, ANNA LIISA LAAKSONEN and J E. SUNELL

From the Ferring AB Forskningslaboratorium, Malmö, Sweden and Children's Hospital, University of Turku, Turku, Finland

The circadian variation for plasmacortisol and the adrenocortical function has been studied in children. The circadian variation has been established by measuring plasma cortisol at 2, 6 and 8 a.m. and about 5.30 p.m. The adrenocortical function has been measured by using the intravenous actidtest (0 1 mg i v sampling at time 0 30 and 60 minutes) In 18 hospitalized children without collagenous diseases, serving as controls, a normal circadian plasmacortisol variation was found in 14 patients

24 cases with collagenous disease have received systemic hormone treatment (mainly corticosteroids). 8 patients show a normal circadian variation whereas 9 cases have a

low circadian variation and additionally 7 patients show a low normal circadian rhythm. In the hormone treated patients 7 cases have normal adrenocortical function. 8 patients have a low adrenocortical function and 5 cases a low normal adrenocortical function.

The study group also includes 16 patients with collagenous diseases without hormone treatment. The circadian rhythm in these patients was normal in 9 high in 1 and low in 6 cases. Adrenocortical function test in this group shows normal function in 10 low function in 5 low normal function in 2 and initially normal function turning into low in 1 patient.

Detailed data will be presented and discussed.

103 FAMILIAL OCCURRENCE OF YERSINIA ENTEROCOLITICA INFECTION AND ACUTE ARTHRITIS

P AHVONEN and TUIRE ROSSI

From the Municipal Bacteriological Laboratory Aurora Hospital, Helsinki and Children Hospital, University of Turku, Turku, Finland

Nonpurulent arthritis with acute onset has been reported in association with *Yersinia enterocolitica* (Y.E.) infection (1). The arthritis usually appears to be transient, but its pathogenesis and long-term prognosis are still largely unknown. In the acute phase the disease may resemble rheumatic fever without endocarditis. In some severe cases electrocardiographic T-wave changes have been noted.

Altogether six cases of arthritis associated with Y.E. infection were observed in two families. Two of five members of family A and four of six members of family B contracted arthritis with acute onset within a period of four months and one month, respectively. In addition, one member of the former family and two members of the latter had only gastrointestinal symptoms (Table 1).

In all symptomatic cases high agglutinin titres against Y.E. were detected in serum specimens obtained two to seven weeks after the onset of the disease. The titres were significantly reduced (at least two twofold dilution steps in parallel tests) within one to four months. Y.E. was isolated from stools of two patients, one of whom had a mixed infection with two Y.E. serotypes. In all other cases the bacterial culture was attempted at a late date or after antimicrobial therapy Y.E. type III was repeatedly isolated from stools of pigs owned by family B

In five cases diarrhoea or abdominal pain preceded the acute onset of arthritis by one to two weeks. In five patients two or more joints were affected with swelling and tenderness, in one patient only one metacarpophalangeal joint. Joints of the feet were involved in four cases, knees and wrists in two Two patients had low back pain and a third showed X-ray changes in the sacroiliac joints with narrowing of the joint space and sclerosis. The affected joints in all other cases were radiologically normal. In two cases with effusion in knee joints the synovial fluid contained 14000 to 63000 leucocytes/mm^3 with 77 to 95 / polymorphonuclears. Bacterial culture of the fluid was negative. ESR ranged from 40 to 121 mm/hour Anaemia and slight leucocytosis were present in two cases. Latex and Waaler Rose tests were

101 SOME ASPECTS OF THE EVALUATION OF LOCAL RHEUMATOID ACTIVITY

P TISELIUS

From the Regional Hospital, Örebro, Sweden

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SCIENTIFIC EXHIBITIONS

Table 1 *Some clinical and laboratory data of nine patients with Y.E infection.*

Case No.	Sex	Age (years)	Abdominal symptoms	Arthritis	Y.E. agglutinins: Serotype (0-antigen)	Maximal titre	Y.E. culture
A 1	M	13	—	+	III	1280	—
2	M	15	+	+	III + IX	1280/2560	+/+
3	M	42	+	—	IX	1280	+
B 1	M	11	+	+	III	320	—
2	M	13	+	+	III	5120	—
3	M	16	+	—	III	2560	—
4	M	18	+	+	III	5120	—
5	F	42	+	+	III	1280	—
6	M	46	+	—	III	320	—

* Y.E. type III isolated from stools of pigs owned by family B

negative in all. Antistreptolysin 0 titre was normal in five cases and 400 in one.

No symptoms or signs indicating carditis were observed in any patient. The electrocardiogram and chest X ray were normal in every case None of the patients had preceding sore throat. In one case erythema nodosum developed before the onset of arthritis. One patient had acute iritis as the first symptom and a second attack of iritis four months later

Antibiotics (tetracycline and/or penicillin) were given to all arthritis patients, but they had no distinct effect on the joint symptoms Intra-articular steroids in two cases had only a transient beneficial effect. In three patients all symptoms subsided within two to seven months, in three others signs of arthritis were still present after two months follow up period

These familial cases provide further evidence of the relationship between Y.E. infection and arthritis. In one family there was the very probable possibility that the infec tion might have been transmitted from pigs, which have been suggested as one possible source of Y.E. infection in man (²). It is impossible to say whether the familial occurrence of arthritis was due to hereditary or other host factors or whether the Y.E. strains in question were arthritogenic.

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1. THE INCIDENCE OF CYTOMEGALOVIRUS INFECTION AMONG INFANTS LESS THAN ONE YEAR ADMITTED TO A PAEDIATRIC DEPARTMENT

H. KERZEL ANDERSEN J. J. GRAVESEN and T. IVERSEN

From the Institute of Medical Microbiology, University of Aarhus, and the University Clinic of Paediatrics, Aarhus Kommunehospital, Aarhus, Denmark

Among 357 infants less than 1 year of age, admitted September 1967 to September 1968 to the University Clinic of Paediatrics, Aarhus Kommunehospital, Denmark, a study was undertaken at admission for the incidence of cytomegalovirus infection by virological and serological methods.

The incidence of CMV infection was about 1 per cent in infants less than 2 months, 6 per cent in infants 2—3 months of age and 24 per cent in the age-group 4—12 months.

A high frequency of seropositivity among infants below the age of 6 months prompted a study of the role of maternal antibodies by comparing the occurrence of CF antibodies in 251 paired mother infant sera. The serological findings indicated that the maternal antibodies against CMV are demonstrable only during the first few months of life. Findings of CMV CF antibodies in infants above the age of 4 months seem to be an expression of infection with this virus. CMV excretion was demonstrated in a total of 14 of 25 infants who were seropositive in the age of 6—12 months.

The clinical manifestations in the infants excreting CMV are mentioned. Half of the patients were admitted due to recurrent or more acute signs of respiratory disease.

2. BREAST FEEDING AND POSTPARTUM CARE

INGRID BJERRE and H. EKELUND

From the Department f Paediatrics General Hospital, Malmo, Sweden

As elsewhere in the West, the frequency of breast feeding in Malmö has fallen during the last decade. In 1958 as many as 60 / of the infants were breastfed for 2 and 28 */ for 6 months, compared with 37 / and 12 *, respectively in 1968. The lying in period has also been shortened, with the result that the mothers have received less instruction in breast feeding and infant care. 1965—67 mothers were usually sent home on the second or third day after an uncomplicated delivery In November 1967 a »semi service ward with rooming in was opened up where the mothers were waited upon less. This offered an opportunity to study the effect, if any of rooming-in on the frequency of breastfeeding.

The series consisted of 3214 mothers with

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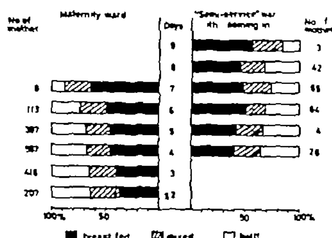


Fig 1 Infants diet at one month in relation to lying in period.

infants and constituted 91 % of all livebirths in the town during a 12-month period. The infants diets were followed up for 6 months by questionnaire at the child welfare centres. The group admitted to the »semi-service ward was compared with the rest of the series. The former group constituted 13 % of the entire material and included an over representation of primiparae, young mothers and unmarried mothers. The average lying in period was 6 7 days compared with 4.3 for the rest of the series

93 % of the women in the rooming in group nursed their children when leaving hospital compared with 76 % of the mothers in the ordinary maternity ward At 1 3 and 6 months the difference was not significant.

In the material as a whole breast feeding was somewhat more common among the primiparous than among the multiparous women, and less common among mothers below 20 years and among unmarried mothers. Breast feeding was more common among mothers who spent more than 4 days at the department irrespective of the group to which they belonged. Feeding difficulties, especially constipation and crying were more common among the infants that were bottle fed. Only in 1—2 % was breast feeding discontinued because of such symptoms.

The duration of breast feeding was not significantly longer among the mothers in the rooming in group than among those in the ordinary maternity ward. On the other hand, the former group had more self confidence in the management of their children and sought advice less often at the child welfare centre during the first month after delivery

The frequency of breast feeding is dependent on several factors. We feel, how ever that adequate care at the maternity ward, where the mother has a good opportunity not only to rest after parturition but also to get to know her child under expert advice, has a favourable effect on breast feeding and management of the child in general.

This investigation has been published in detail elsewhere (1)

1 Bjerre I. & Ekelund, H. Amning och BB-vård. *Läkartidningen* 67 1970 to be published.

3 CARDIAC CATHETERIZATIONS ON CHILDREN AT CARDIO-RESPIRATORY RESEARCH UNIT UNIVERSITY OF TURKU

M. DAHL, L. HIRVONEN and T PELTONEN

From the Cardiorespiratory Research Unit, University of Turku, Turku, Finland

Between 1956 and 1970 the Cardiorespiratory Research Unit carried out ca. 1150 catherizations of the right heart, including about 850 on paediatric patients. The distribution of the diagnoses in the paediatric series was as follows (Table 1)

Table 1.

Diagnosis	Age		Total
	1 year	1—15 years	
Atrial septal defect (ASD)	18	115	133
Open foramen ovale	4	33	37
Ventricular septal defect (VSD)	24	139	163
ASD + VSD	14	22	36
Pulmonary stenosis	4	69	73
Fallot	7	29	36
Patent ductus arteriosus	12	114	126
Aortic coarctation or stenosis	14	32	46
Miscellaneous	28	53	81
Functional murmur or normal	7	114	121
Total	132	720	852

The series contained 45 per cent boys and 55 per cent girls. Angiocardiography was performed in 72 per cent of cases in the age group $<$ 1 year. The corresponding figure for the older age group was 25 per cent. About 40 per cent of the catheterized children were operated at the Department of Surgery of Turku University. Several more were operated after they had reached the age of 16 years. The mortality rate within the first 24 hours after catheterization with angiocardiography was 0.3 per cent in the age group of 1 to 15 years and 6 per cent in the age group of $<$ 1 year. Two patients died immediately on examination.

4. PERINATAL MORTALITY IN HELSINKI

M. J. FIRMILÄ, M. KAUPPINEN, T. KOLI, A. NEDRUM, C. E. RÄIHÄ, L. TERVILÄ, C. E. UNNÉRUS, E. VARTIAINEN and V. VÄYRYNEN

From the Departments of Obstetr. Gyn. Department of Paediatrics of the University and from the City Health Department of Helsinki, Helsinki, Finland

In 1954, Räihä suggested that fetal growth and the duration of pregnancy (prematurity) is dependent on uterine blood flow and consequently on maternal circulatory capacity. In healthy women this capacity can be estimated by measuring maternal blood volume or heart volume (Sjöstrand, Reindell et. al.)

It is shown in this paper that in healthy mothers uterine blood flow before parturition is significantly reduced if the heart volume is small.

It is also shown that by the introduction of measurement of heart volume and of advice to rest daily if the heart volume is small, perinatal mortality can be reduced from 2.5 per cent to 1.3 per cent. The difference in mortality is due to reduced incidence of newborn babies with a low birthweight. Furthermore, the rates of pre-eclampsia, and prematurity in twin births are presented and the effect of social groups on mortality is demonstrated.

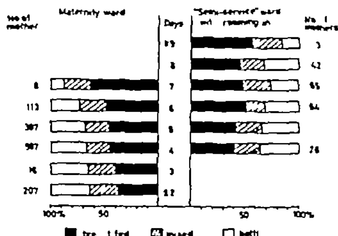


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In the material as a whole breast feeding was somewhat more common among the primiparous than among the multiparous women, and less common among mothers below 20 years and among unmarried mothers. Breast feeding was more common among mothers who spent more than 4 days at the department irrespective of the group to which they belonged. Feeding difficulties, especially constipation and crying were more common among the infants that were bottle fed. *Only in 1—2 % was breast feeding* discontinued because of such symptoms.

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for date» In three patients the hypoglycaemia lasted for more than 12 hours, all of these being small for date»

In singletons born to mothers without toxaemia, there was no significant difference as to frequency of hypoglycaemia between »small for date»-infants and those with birth weights above the 10th percentile. However hypoglycaemia lasting for more than 12 hours occurred twice as often in small for date»s as compared to the others (7 / and 3 /› respectively).

In 20 pairs of twins, *simultaneous blood glucose determinations were compared in the larger and the smaller* twin. In 7 pairs of twins with a difference in birth weight of more than 250 g (260—1170), the average blood glucose in the larger infant was 46.0 mg/100 ml as compared to 31 0 mg/100 ml in the smaller one.

In 13 pairs of twins with a birth weight difference of less than 250 g, there was no difference in blood glucose between the larger and the smaller twin (41 0 mg and 42.0 mg per 100 ml respectively).

8. PERINATAL MORTALITY IN NORWAY

G FLUGE and A. SUNDAL

From the Department of Paediatrics, University f Bergen, Bergen, Norway

The stillbirth rate, mortality in the first week of life and that in the first year are presented for th years 1935/40 to 1968 (Table 1 and 2.)

In these thirty years has the stillbirth rate declined from 22 5 to 11 1 per thousand births. Mortality in the first week of life has decreased from 16 to 8.8 per thousand live births. Thus the perinatal mortality (stillbirths + deaths in the first week) has been reduced from 38.5 in 1935/40 to 19.9 per thousand births in 1968

The causes of death were

Table 1 *Stillbirths*

Bergen 1967—1968—1969	Birth weight: Under 2500 g	Birth weight: Over 2500 g	Total
Pathology related to umbilical cord/ placenta	20	23	43
Pathology t birth	14	15	29
Pathology in the mother	19	6	25
Pathology in the foetus	4	12	16
Uncertain causes	19	17	36
	76	73	134

Table 2. *Deaths in the first week of life*

Bergen 1967—1968—1969	Birth weight: Under 2500 g	Birth weight: Over 2500 g	Total
Pulmonary complications	63	15	80
Intracranial hemorrhage	12	8	20
Marformation	2	10	12
Infection	6	4	10
Erythroblastosis foetalis	4	1	5
Neuroblasma	0	1	1
Uncertain causes	4	1	5
	93	40	133

5 BIRTH WEIGHT/GESTATIONAL AGE IN PREMATURE NEWBORN INFANTS

Influence of Toxaemia of Pregnancy Small for Date Newborn Infants Neonatal Hypoglycaemia.

G FLUGE and A. SUNDAL

From the Department of Paediatrics University of Bergen, Bergen, Norway

In the Children s Hospital Bergen, gestational age and birth weight have been registered in all patients admitted with a birth weight of 2500 g or less in the years 1967—1968—1969 The results have been plotted against the Lubchenco percentile scheme showing the foetal weight according to gestational age. (Table 1)

Our material consists of 323 newborn infants. Sixty-one were twins or triplets — which have been excluded as their foetal weight deviate from those of singletons The material, therefore consists of 262 singletons. Forty of these infants were born to mothers with toxaemia of pregnancy while 222 were born to mothers without toxaemia.

Sixteen out of 40 newborn infants (40 %) born to toxaemic mothers had birth weight/gestational age above the 10th percentile while 24 (60 %) were below the 10th percentile (»small for date)

Amongst 222 singletons born to non toxaemic mothers 178 (80 %) had birth weight/gestational age above the 10th percentile while 44 (20 %) were small for date»

Evaluation of hypoglycaemia in premature newborn infants (blood glucose below 20 mg. per 100 ml during the first 72 hours) showed that 40 toxaemia mothers gave birth to 12 hypoglycaemics, ten of which were small

Table 1

Children s Hospital, Bergen, 1967—68—69	Number	Percentiles. Birth weight/ gestational age (Lubchenco et al)	Hypo-glycaemia	Hypoglycaemia lasting	
				< 12 hours	> 12 hours
Toxaemia of pregnancy	40	Over 10th perc. 16 (40 /)	2	2	0
		Under 10th perc. 24 (60 %) (small for date»)	10	7	3
Twins/ triplets	61		3	2	1
Singleton (non toxaemia mothers)	222	Over 10th perc. 178 (80 %)	27	21	6
		Under 10th perc. 44 (20 /) (small for date)	7	4	3
	323		49	36	13

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G FLUGE and A. SUNDAL

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In the Childrens Hospital Bergen, gestational age and birth weight have been registered in all patients admitted with a birth weight of 2500 g or less in the years 1967—1968—1969 The results have been plotted against the Lubchenco percentile scheme showing the foetal weight according to gestational age (Table 1)

Our material consists of 323 newborn infants. Sixty-one were twins or triplets — which have been excluded as their foetal weight deviate from those of singletons. The material, therefore, consists of 262 singletons. Forty of these infants were born to mothers with toxaemia of pregnancy while 222 were born to mothers without toxaemia

Sixteen out of 40 newborn infants (40 %), born to *toxaemic mothers* had birth weight/gestational age above the 10th percentile while 24 (60 %) were below the 10th percentile (small for date)

Amongst 222 singletons born to *non toxaemic mothers* 178 (80 %) had birth weight/gestational age above the 10th percentile while 44 (20 %) were small for date»

Evaluation of *hypoglycaemia* in premature newborn infants (blood glucose below 20 mg per 100 ml during the first 72 hours) showed that 40 toxaemia mothers gave birth to 12 hypoglycaemics, ten of which were small

Table 1

Childrens Hospital, Bergen, 1967—68—69	Number	Percentiles. Birth weight/ gestational age (Lubchenco et al.)	Hypoglycaemia	Hypoglycaemia lasting	
				< 12 hours	> 12 hours
Toxaemia of pregnancy	40	Over 10th perc. 16 (40 %)	2	2	0
		Under 10th perc. 24 (60 %) (small for date)	10	7	3
Twins/ triplets	61		3	2	1
Singleton (non toxaemia mothers)	222	Over 10th perc. 178 (80 /)	27	21	6
		Under 10th perc. 44 (20 %) (small for date»)	7	4	3
	323		49	36	13

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Scientific research is focused on the physiology of circulation and on clinical physiology in the foetal and neonatal period. In 1964, the National Medical Board classified the Cardiorespiratory Research Unit as a research institute conforming with the Act on Private Medical Establishments. In 1965, by a university ordinance, it was made an official Turku University Institute.

9 IgG LEVELS IN MATERNAL AND CORD SERA AND THEIR RELATIONS TO BIRTH WEIGHT AND GESTATIONAL AGE IN VARIOUS GROUPS OF NEWBORN

MARJAANA HAUTALA and MARJATTA KUNNAS

From the Central Hospital, Tampere, Finland

Determination of IgG concentrations has been made using the radial immunodiffusion technique according to Mancini. The material consists of 306 mother-child samples. The gestational age varied between 23 and 44 weeks (187 infants ≤ 37 weeks) and birth-weight between 600 and 4600 grams (107 infants weighing ≤ 2500 grams). 15 twins and 19 cesarean sections were included in the material. No difference in IgG levels could be observed in these groups as compared to the material as a whole.

IgG content in cord serum and especially its ratio to maternal IgG content was found to correlate remarkably well with duration of pregnancy. The correlation with birth weight was not quite so good. These results were obtained statistically using regression analysis and correlation diagrams.

10 A FAMILY WITH A PRESUMPTIVE C/F TRANSLOCATION

T KLINGE and A J THERKELSEN

From the University Clinic of Paediatrics, Aarhus Kommunehospital and the Institute of Human Genetics, University of Aarhus, Aarhus, Denmark

The pedigree of a family investigated cytogenetically in four generations is presented together with karyotypes of the propositus and his father. The karyotype could be described as 46, $F-$ $E_{18}+$ in both cases and a further 15 members of the family had the same abnormal karyotype. All living members of the family were pheno-

During the same years the infant mortality in Norway has declined from 39.5 to 13.7 per thousand live births.

In the years 1967—1968—1969 *post mortem* examinations have been undertaken (Department of Pathology, University of Bergen. Head Professor Erik Waaler) in all *stillbirths* (Maternity Hospital, Bergen) and in all *early neonatal deaths (first week of life)* (Children's Hospital, Bergen)

7 HEMODIALYSIS IN INFANCY WITH AN ARTIFICIAL KIDNEY TYPE ALVALL

N. HALLMAN, M. PASILA, P. MÄKELÄ, J. VILSKA and T. AHOLA

From the University Central Hospital Helsinki — Children's Hospital, Helsinki, Finland

A Kill type disposable dialyser with low priming volume has been used in dialysis of small infants. A parallel roller pump used in the inflow and outflow has made it possible to overcome the resistance of the small bore indwelling silastic canulas. With the vein to vein system the blood flow has been from 20 to 50 ml/min. The mean ultrafiltration of 60 ml in an hour has been recorded with a negative pressure of 100 mm Hg. A dialysis from 4 to six hours has been performed every other or every third day in the patients without their own kidney function.

8 HISTORY OF THE CARDIORESPIRATORY RESEARCH UNIT OF TURKU UNIVERSITY IN 1956—1970

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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]		[illegible]
[illegible]	[illegible]			[illegible]
[illegible]	[illegible]		[illegible]	[illegible]
[illegible]	[illegible]		[illegible]	[illegible]
[illegible]	[illegible]			[illegible]
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The patient is the first child in the family and was born at 38 weeks after a normal pregnancy The birth weight was 2700 g Both parents are normal. There is no family history of cyanotic disease The parents are unrelated

At birth the baby was cyanotic. The colour was only slightly improved by oxygen. On admission to the paediatric department in Oulu the child was cyanotic but not distressed

At first the infant was suspected of having cyanotic congenital heart-disease, but, in view of the lack of positive evidence of heart-disease, the adequate aeration of the lungs, the absence of distress and normal PO_2 tension in arterial blood, it was decided to examine the blood for methemoglobin.

The blood was chocolate brown and the colour was not changed by shaking with air The total blood-pigments were 17 4 g hemoglobin/100 ml, of which 38 per cent was methemoglobin, determined by the method of Evelyn and Malloy (1)

Hemoglobin electrophoresis was normal. Diaphorase activity measured by the method of Scott was 1 1 units O.D./min/mg Hg· normal values 6 3 (3 9—15 0) units O.D./min/mg Hg (3)

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Subject	Age yrs.	[illegible]	Diaphorase [illegible]	Interpretation
Propositus	[illegible]	[illegible]	.1	homozygote
Mother	[illegible]		1.	heterozygote
Father	[illegible]		1.	heterozygote
Paternal aunt	16			normal
uncle		[illegible]	[illegible]	heterozygote
grandfather	47	[illegible]		normal
grandmother	44		1.	heterozygote
Maternal uncle	11		1.	heterozygote
uncle	[illegible]		4.	normal
grandfather			.1	normal
grandmother	41			heterozygote

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At first the infant was suspected of having cyanotic congenital heart-disease but, in view of the lack of positive evidence of heart-disease the adequate aeration of the lungs, the absence of distress and normal PO_2 tension in arterial blood, it was decided to examine the blood for methemoglobin.

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a nearby building which had formerly been a mental hospital became a 70-bed children's department. On May 1st 1938 Dr Kyrki was appointed superintendent of the children's department, and at this time the first children's hospital was closed down. Aino Lidman, matron of the former children's hospital, became head of the children's department.

In the following year 1939 part of the children's department was taken over by the military hospital, and only 38 beds remained. The hospital management's lack of understanding of and indifference to the most basic requirements of child care had grave repercussions in 1940 all premature babies admitted to the hospital died, this mortality falling below 90 per cent only after the war

From the beginning of 1945 the children's department of the Turku County Hospital became the University Children's Clinic. Dr Kyrki was appointed pro tem. professor On August 28th 1945 Toivo Salmi was appointed the first professor of paediatrics In the same year the children's clinic was given back the beds taken over temporarily by the military hospital. Some structural repairs were also made at this time. In the 1940's the most frequent disease was diarrhoea, 40 per cent of infants being affected. Between 1939 and 1949 respiratory tract infections, tuberculosis, diarrhoea, and prematurity caused the death of 75.9 per cent of all infants admitted to the children's clinic, every fourth death occurring during the first 24 hours after admission. The interior of the clinic was reconstructed so that the old clinic finally consisted of four wards and a polyclinic. The completion in 1942 of the City Hospital for Infectious Diseases was of decisive importance for child care in Turku. Dr Johan Wickström, who was the first docent of our medical faculty was appointed head physician of this hospital.

The Hospital for the Swedish-speaking district round Turku, which has a children's ward of 30 beds, was completed in 1951 Olle Palmberg was head physician of this hospital until his death (1969). Dr Kalevi Korttila (died 1963) introduced child surgery to Turku.

The Children's Heart Polyclinic was started in 1953 and in 1956 in co-operation with the University Heart Examination Centre, it was possible to begin cardiac catheterizations and angiographies. Systematic child psychiatry was begun in 1962, when the position of part time specialist was created. This was made a full-time position in 1966

Professor Salmi, professor of paediatrics since 1945 died in 1965 and was thus unable to see the completion of the new University Clinic. This new clinic offered facilities for child rheumatology and the various aspects of child neurology In its present form the children's clinic consists of 188 beds 120 for children's internal diseases, 54 for surgical patients and 14 for psychiatric patients. In addition there is an intensive care unit for six patients, a surgical department, a children's ward for clinical physiology which is also a heart clinic, and a neurophysiologic laboratory

Thus there has been a children's hospital in Turku for 50 years, while the University Children's Clinic has been in existence for 25 years. The University Clinic has produced about 500 studies, 16 of them theses.

18. ANTITOXIN RESPONSE TO BOOSTER DOSE OF WEAK AND NORMAL DIPHTHERIA VACCINE

E. RABO

From Gothenburg Sweden

been found in about 50 % of all full term newborns and stillborns. After the age of 9 months, these calcifications can be seen grossly in all cases. Presumably the early selective calcifications in the common and internal iliac arteries are the result of a high blood volume lead on these arteries during fetal life. Another vessel which is often affected by calcification is the siphon of the internal carotid artery In this segment calcifications can usually be found in children over one year of age They first appear in the upper part of the siphon at the origin of the ophthalmic artery

14 TWO CASES OF AMPICILLIN RESISTANT MENINGITIS CAUSED BY HAEMOPHILUS INFLUENZAE

K. NIEMI and TUULA HUUPPONEN

From the Central Hospital, Tampere Finland

15 CYTOMEGALIC INCLUSION DISEASE IN CHILDHOOD

K. NIEMI and TUULA HUUPPONEN

From the Central Hospital, Tampere Finland

16 TRICHOMONAS INFECTION OF THE NEWBORN INFANT

K. NIEMI and TUULA HUUPPONEN

From the Central Hospital, Tampere Finland

17 50 YEARS OF CHILDREN'S HOSPITAL IN TURKU

T PELTONEN VIRPI KINNUNEN ANJA KIVILAAKSO and AINO LIDMAN

From the Children s Hospital, University of Turku, Turku Finland

In 1919 a children s hospital of 15 beds was established in Turku by an association called »For the Children This was the first children s hospital in the country outside Helsinki. It was founded and managed by a doctor Rafael Kyrki, assisted by a nurse, Aino Lidman. When the main building of the Turku County Hospital was completed,

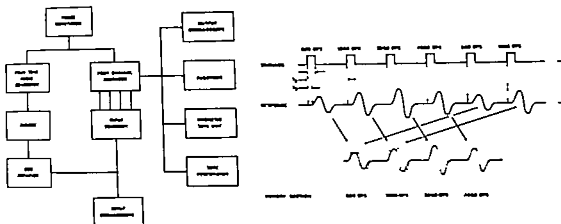


Fig 1. The four channel averaging system for ERA.

Fig 2 Typical evoked responses, A 22 year-old male, B. 7 year-old boy The sweep duration is 800 msec, the predelay 100 msec. The left side of figure shows the response of four different stimulus frequencies which are summed up on the right side

stimulating the patient and, on the other hand, triggers the averaging unit (Intertechnique Didac 800). The patient receives t regular intervals (T_2 = 1,5 sec) pure tone stimuli which cause an electric response after the latency T_3. The amplified signal can be seen on the oscilloscope screen and is fed in the averaging unit. Its memory is

19 A DIP SLIDE AT HOME PERFORMED URINE CULTURE — A SAFETY MEASURE AFTER CHEMOTHERAPY IN URINARY TRACT INFECTIONS

LIISA RAUTALAPPI, P MÄKELÄ and L KANTERO

From the Children's Hospital University of Helsinki, and Aurora City Hospital, Helsinki, Finland

A report is given of a cumulative study consisting mainly of primary infections. The individual 8-month post infection follow up period consists of weekly urine cultures at home or immediately if there are general symptoms. This is made possible by teaching the parents to perform the cultures and relate them to the reference corresponding to 10^4 colonies per ml Hospital outpatient visits at 2 4 and 8 months or immediately when a positive culture (more than 10^4) appears in the post infection period have been controls for the home made cultures. From the 56 patients most of whom are still under control there have been so far 8 positive cultures at home two of which have shown to be wrong positive. There have been two positive cultures at outpatient visits which have not been discovered at home. The method seems to be a valuable aid for better control of urinary tract infections in families with sufficient cooperation and intelligence.

20 FOUR CHANNEL SYSTEM FOR ELECTRIC RESPONSE AUDIOMETRY (ERA)

A SALMIVALLI M. SILLANPÄÄ, P NURKKANEN and H. LANG

From the Otolaryngological University Clinic Turku, Finland

With modern measuring techniques it is possible to recover weak signals from noise The averaging method is a powerful tool here. This method can be used with the following restrictions 1 the signal to be measured must be electrical, 2 the phenomenon must be repetitive and 3 a trigger pulse locked to the signal must be available Noise can be considered to include all disturbing factors which interfere with the signal.

The averaging unit samples the signal (*e g* one sample per msec) and stores a quantity which is proportional to the signal value at the sampling moment, in the memory unit corresponding to the sampling moment. When the memory unit has received the respective information, the same sequence of events is repeated after the following trigger pulse The new information is added with the former memory content. Within every sampling phase the signal components, locked to the trigger pulse are amplified and the components, not synchronized with the trigger in short noise are gradually rejected. The resulting signal noise-ratio increases with sampling times.

In following we are attempting to explain the averaging method applied to electric response audiometry (ERA) The pulse generator in the averaging apparatus (Fig 1) activates the four frequency audio generator

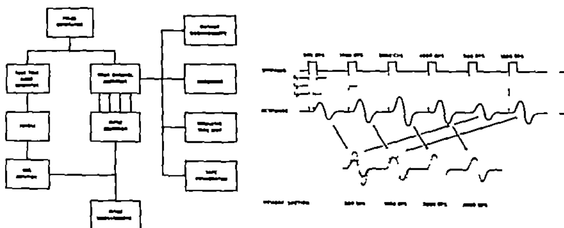


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Case 2.

J N A boy 2.6 years old, born July 1967 two weeks postmature, with a birth weight of 2800 g. Somewhat retarded mental and motor development. Ears mildly black-slant ing, no other cranial or facial anomalies. Syndactyly between III—IV digits on both hands and the right foot. Muscular hypotonia, hemiatrophy on the left side and retarda tion of the bone age eight months. Chromosomes of the parents normal. The patient's chromosomes analyzed from blood cultures, bone marrow lymph nodes and skin biopsies.

Case 3

J E. A boy 5 years old, born April 1958 at term with a birth weight of 3500 g. Severe psychomotor retardation. Microcephaly short neck, short limbs, small jaw protuberant ears with preauricular fistela. Big toes, hammer shaped and medially deviating. Congenital heart disease. Cryptor chismus Muscular hypotonia. Chromosomes analyzed from blood cultures.

Case 4

C W A boy 5 years old, born April 1958 at term with a normal birth weight. Microcephaly mental and motor retardation. Prow-shaped fleeting forehead, capillary hemangiomata on forehead and scalp. The right external ear very large, long, narrow poorly differentiated, with preauricular fistel. Proptosis and heavy lashes. Narrow high arched palate and thick gingival ridges. Flexion anomalies of thumbs, dislocated right hip. Chromosomes analyzed from blood cultures and skin biopsies.

Chromosomal analysis revealed in all cases a similar karyotype of two cell lines: 90—95 per cent contained 46 and 5—10 per cent 45 chromosomes. Karyotypes with 46 chromosomes were normal 46 XY The cells with 45 chromosomes showed only 14 instead of 15 members in C-group. Thus, the karyotype was 45 XY C- So far in repeated studies, the proportions of the two cell-lines have been constantly the same

Autosomal monosomy in man has been considered invariably fatal. Mosaicism may however be compatible with life, if the proportion of the aberrant cells is sufficiently low In such a case, the person may not show severe anomalies. In our patients, the most frequent clinical features were mental and motor retardation, anomalies of face, ears and limbs and, in addition, muscular hypotonia. All of these abnormalities are present in most of the known chromosomal disorders. Thus, it is hardly possible to correlate the clinical features with the cytogenetic findings. It may be that all the chromosomes lost in our cases are the same member of the C-group. Noteworthy is the fact that the missing chromosome might occasionally be an X. In our case 2 the hemiatrophy was remarkable. So far how ever the chromosome analysis has not revealed any differences on either side. The proportion of the abnormal cells may change with advanced age, as is known in trisomy mosaics. The data available at present on our patients do not, however disclose any variation.

divided into four sections (200 memory units in each) one section for every stimulus frequency Because the latency is constant with a definite stimulus intensity the electric response signal is synchronized with the trigger pulse and hence it is amplified out from the background activity The averaged results are made available by means of the output oscilloscope, X Y recorder tape recorder and tape perforator

The miniature earphones, with insert type or individual earplugs, are light and comfortable to use They are easily fixable and the sound intensity remains constant throughout the *measuring time and is unaffected* by movements of head.

Silver cup electrodes are fixed by adjustable vacuum. The DC resistance is usually low (1—3 kΩ) The fixation of electrodes is quick and comfortable for the patient.

The stimulus is pure tone with duration of 200 msec It is given in four different frequencies (500 1000 2000 and 4000 cps) at 1.5 sec intervals. The same frequency is then repeated every 6 sec. The stimulus intensity can be selected with 5 dB steps from —10 dB up to +110 dB

Fig 2 shows typical results The electric response complex of P_1-N_1 P_2-N_2 is clearly noticed in adults (Fig 2A) The electric response of children in school age often shows accumulation The complex of N_1 P_2N usually melts into a long large amplitude response (Fig 2B)

As possibilities of employing this method, the following can be mentioned. 1 usual threshold determination 2. fitting of hearing aid for infants and to localize hearing defect, 3 study of central auditory pathways and 4 comparison *of cochlear* and vertex potentials.

The four channel system has some typical characteristics 1 The apparatus is relatively expensive and technically complicated. 2. Non-cooperating patients (e.g infants and young children, mentally retarded and simulants) can be examined. 3 One frequency *result is controlled by that of three other* frequencies. 4 Results of different frequencies in the same measurement are comparable with each other because the vigilance state is the same for all frequencies. 5 Steadily alternating different frequencies adaptation can be eliminated and nearly maximal response obtained.

21 MOSAICISM OF C-CHROMOSOME (6—12), 46 XY/45 XY C—

Report of Four Cases

M. SILLANPÄÄ and ANNA LIISA SALONIUS

From the Children's Hospital and Department of Genetics University of Turku Turku, Finland

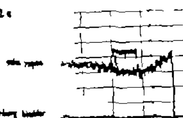
Mosaicism of autosomal monosomy has rarely been described. This is a report of four cases of C-group chromosome monosomy mosaicism with congenital anomalies.

Case 1

E N A boy 1.5 years old born December 1968 at term with a birth weight of 3850 g Mild mental and motor retardation. Hoarse, weak voice large tongue, bloated face an unusually broad jaw small nose with a low ridge Muscular hypotonia, loose ligaments, *subluxation of joints* and inspiratory stridor *Height normal for age*, no genital anomalies. Chromosomes analyzed from repeated blood cultures.

Table 1. *Relationship between the result of the Hippuran ¹³¹J test and the findings on clinical examination and surgical exploration of flow of the ventriculocardiac shunt.*

Hippuran ¹³¹J test		Clinical findings			Obstruction verified at re-operation
		Obstruction	Uncertain	N obstruction	
Obstruction	6	5	1		6
Uncertain	3			3	
N obstruction	15	2	4	9	
Total	24	7	5	12	6



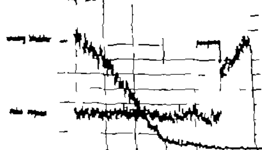


Fig. 2a. Typical finding in a case of total obstruction of the ventriculocardiac shunt.

Fig. 2b. Free flow in the same patient after re-operation.

The Hippuran test indicated free flow in 15 cases. In nine of these clinical examinations indicated free flow obstruction was suspected in four and was felt to be definite in two cases.

The function of ventriculocardiac shunts can be assessed by means of the Hippuran ¹³¹J test. The test can be considered reliable. In our study there were no false positive results. Free flow could be demonstrated in two cases, where the shunt based on clinical examination was found to be obstructed, and thus an unnecessary re-operation was avoided.

The test is most useful in the group of patients with clinically suspected, but not unequivocal obstruction of the shunt. In all cases in this group the Hippuran test solved the problem. The test is not reliable in localizing the site of the obstruction. If the *isotope is injected into the cerebral ventricles*, where it is diluted by the cerebrospinal fluid, the transfer of the radioactivity to the urinary bladder is slow and the test results are less reliable. We have abandoned this method.

The Hippuran test is a simple procedure which can be carried out on an outpatient basis without any special preparation of the patient. It gives good information on the function of the shunt and can easily be repeated. Since the test can be performed rapidly and safely it will be adapted for routine use at our hospital for assessment of the function of ventriculocardiac shunts.

22 VENTRICULOCARDIAC SHUNTS IN HYDROCEPHALIC CHILDREN TESTING WITH HIPPURAN ¹³¹J

M. SILLANPÄÄ T TÖRMÄ, T PÄRVINEN and P MÄKELÄ

From the Children's Hospital and Department of Radiotherapy and Unit of Neurosurgery of the Department of Surgery University of Turku, Turku, Finland

Among the most common disturbances of the function of ventriculocardiac shunts is obstruction of flow A block can be suspected from anamnestic, physical, X ray and echo findings and can be verified at operation. Since we have not been able to unequivocally confirm the obstruction of flow before surgical exploration of the shunt, and since unnecessary operations may be harmful we have made an attempt, during the last year to determine the patency of the shunt using radio isotope Hippuran ^{131}J

The study was performed altogether 24 times on 15 patients. On clinical findings obvious obstruction was present in seven cases and possibly present in another five. The radiological studies consisted of plain skull films and sometimes additional chest X rays. The echo studies were made utilizing A and B-echoencephalography In 22 cases the shunt studied was a Spitz Holter valve and in two cases a Pudenz valve. Hippuran ^{131}J (10 μCi) was injected into the Rickham reservoir if present, or into the valve The disappearance of the radioactivity from the valve system was monitored by one detector and the appearance and increase of radioactivity in the urinary bladder by another one (Fig 1a and 1b) The effect of pumping the valve on the transfer of radioactivity was also investigated Fig 2a presents the curve obtained in a patient with obstruction of the shunt, and Fig 2b the curve obtained from the same patient after revision of the shunt. None of the patients exhibited any signs of renal or cardiac insufficiency

The results are presented in Table 1. The Hippuran test revealed an obstruction in six cases and the obstruction was confirmed in all of them at re-operation. The test gave an equivocal result in three cases, in which the clinical examinations indicated free flow Obviously parts of the radioactive isotope had been deposited outside the Rickham reservoir

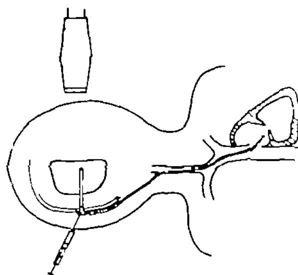


Fig 1 a. Application of radioactive isotope into the Rickham reservoir

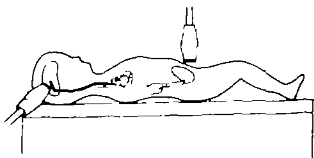


Fig 1 b Placement of the detectors during the test.

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23 ACCELERATED MATURITY IN FETAL THYROTOXICOSIS

S SIMILA and L ANTTOLAINEN

From the Department of Paediatrics University of Oulu, Oulu, Finland

Before birth, thyroid hormones are vital to fetal maturation, but their influence on growth is uncertain (1) What is the effect of an excess of thyroid hormones on fetal development in cases of congenital thyrotoxicosis?

The etiology of congenital thyrotoxicosis is shown to be the long acting thyroid stimulator (LATS) produced by mother LATS being an immunoglobulin G passes the placenta and induces fetal hyperthyroidism by steady stimulation of the fetal thyroid gland (3)

Data for this study are collected from the literature (23 cases) and added to our own three cases of congenital thyrotoxicosis. Birth weights (26 cases) and birth lengths (10 cases) are plotted against the normal intrauterine growth curves of Lubchenco et al (2) the most commonly used international curves.

The mean gestational age of these 26 cases was 35 3 ± 4 1 (S.D) weeks and the mean birth weight 2 321 ± 580 g The mean birth length of 10 cases was 46.9 ± 3 8 cm (the mean gestational age of these 34 4 ± 3 7 weeks) and the mean weight length ratio $(\frac{100 \times \text{weight}}{\text{length}^3})$ was 2.24 ± 0.21 (Fig 3)

Fig 1 and 2 demonstrate that birth weight and length differ from the mean in direct proportion to length of pregnancy The weight length ratio figure also supports this observation.

Bone age is given only in 10 cases, the mean at birth being 2.3 months. When gestational age is taken into account, bone age is 3.9 months more advanced than chronological age

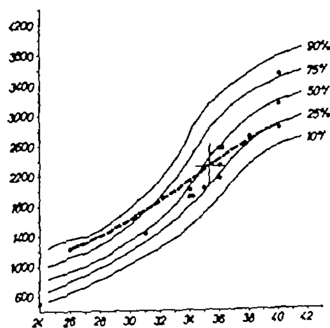


Fig 1 Birth weights in cases of congenital thyrotoxicosis (+ Mean and S. D ——— Estimated mean curve)

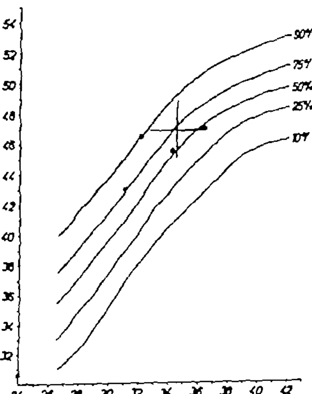


Fig. 2 Birth lengths in cases of congenital thyrotoxicosis (+ Mean and S. D.)

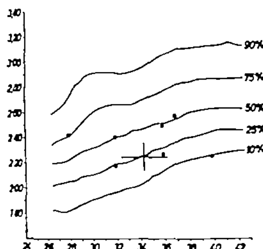


Fig 1. Birth weight-length ratios in cases of congenital thyrotoxicosis (+ Mean and S. D.).

The neurologic maturity of our three cases (gestational ages 36 37 and 32 weeks) is that of a full term normal newborn.

All these findings
- — low gestational age
- — low weight length ratio
- — advanced skeletal development
- — advanced neurologic maturity

suggested accelerated maturity in fetal thyrotoxicosis. The low birth weight after 36 gestational weeks may suggest relative placental insufficiency the fetal hypermetabolism exceeding the capacity of the placenta. Unfortunately weight of placenta is given only in three cases. In these the mean relative weight of placenta $\left(\frac{100 \times \text{weight of placenta}}{\text{birth weight}}\right)$ is 28.6 per cent. It may suggest slight placentomegaly in fetal thyrotoxicosis.

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24 CHIMERISM IN TWO BOYS WITH CONGENITAL ABNORMALITIES

A. J THERKELSEN and T IVERSEN

From the Institute of Human Genetics, University of Aarhus and the University Clinic of Paediatrics, Aarhus Kommunehospital, Aarhus, Denmark

Most cytogenetical investigations are performed on cultures from blood only Other tissues should be investigated in all cases where a discrepancy is found between the clinical manifestations and the cytogenetical findings in blood. With the purpose of emphasizing this two cases of chimerism are presented one is 46,XY in blood and 47,XY F+ (or possibly 47,XY t(GqGq)+) in skin, the other is 46,XY Gp- in blood but a mosaic in skin, presumably of the type 46,XY Gp-/45,XY t(GqGq)+ The clinical manifestations and photos of the two boys are presented together with chromosome counts and karyotypes in the blood and skin.

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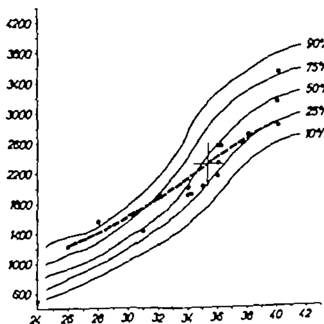


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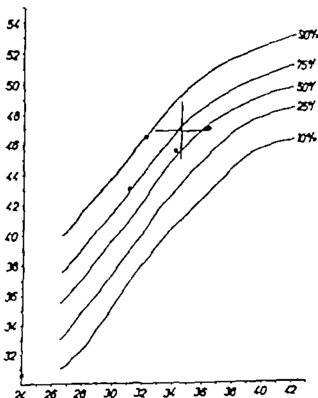


Fig 2 Birth lengths in cases of congenital thyrotoxicosis (+ Mean and S. D.)

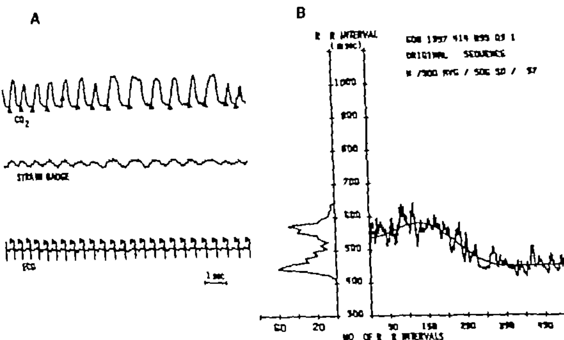


Fig 2. (A) Generation of point processes (event detection) from the CO_2 respirogram and the ECG A computer display with arrows indicating the detected events is provided for immediate visual verification in case of abnormal variation. (B) Sequential R R interval histogram superimposed by Chebyshev approximation of the original data. The corresponding interval distribution curve is shown on the left.

nomials was used to compute the approximated function Y in the following form.

$$Y = \sum_{i=1}^{6} C_i T(x)$$

where C_i represents the calculated coefficient, and $T_i(x)$ is the corresponding Chebyshev polynomial.

In this type of numerical approximation the first coefficient, C_0, represents the mean value of the intervals. C_1 represents the general slope of the function, C_2 represents the degree of convexity etc In this fashion the six coefficients represent a remarkably concise description of slow variability and trend in the spike train (7).

The data shown in Fig 2B represent a sequence of 500 R R intervals in a normal infant demonstrating the level of variation observed on the average in normal groups of subjects such as reported previously by Tario (7) During the time represented in this graph (about 4 minutes) the heart rate increased resulting in the bimodal interval distribution shown on the left, and the marked s shaped approximation shown on the right.

The same procedures were used to represent interval variation in the E-E interval sequence derived from the CO_2 respirogram. Because of the irregularities often observed in the form of the CO_2 curve, more serious technical difficulties were met in deriving the E-E interval sequence. Therefore a visual check of the analog CO_2 and strain gauge recordings was performed in all cases with unexpected or unusual patterns in the computer sequential histogram.

Experience gained from the present study and from an earlier study (7) suggests that the methods of computation and display employed are suitable for automatic analysis of the spike-to-spike variation of cardiac and respiratory signals. In addition the use of a Chebyshev approximation appears to be an

25 COMPUTER ANALYSIS OF LONG-TERM RECORDS OF HEART RATE AND RESPIRATION RATE IN NEWBORN INFANTS

I VÄLIMÄKI, P A. TARLO K. E. SCOTT V C UNITE and P M. RAUTAHARJU

From the Department of Physiology and Biophysics Dalhousie University Halifax Nova Scotia, Canada

Variation of heart rate in sinus rhythm is a normal phenomenon found in most full term newborn infants Absence of this variation, so called fixed heart rate pattern is occa sionally present in the long term ECG records of premature infants and this pattern is especially typical in the respiratory distress syndrome (2, 3) Tachycardic and short bradycardic periods, the latter often associ ated with cardiac arrhythmias, are fairly common in all newborn infants (3) Advanced stochastic point process analysis principles have been adapted and employed for charac terization of the statistical properties of sequences of cyclic events (1 2) In this study statistical methods of this type have been applied to quantitate heart rate and respiration rate variations in newborn in fants.

In a pilot project signals obtained from exhaled CO_2, abdominal strain gauge measurement, and the ECG of a group of 20 full term infants were simultaneously recorded on magnetic tape. The original analog records were converted to computer readable digital form with an analog to digital (A/D) converter (Fig. 1) Two spike trains were generated through digital computation from the R R intervals of the ECG and from the expiration-expiration (E-E) intervals of the CO_2 (Fig 2A) This strain gauge signal was utilized in the visual checking of the CO_2 respirogram.

Figure 2B shows an example of the graphical representation used to summarize the events of a spike train in every recording The graph on the right is a sequential R R interval histogram which is a plot of interval duration (msec) against interval number The beat to-beat variability is most easily demonstrated with a display of this type. The graph on the left is a conventional non-sequential (order independent) histogram of the same train of R R intervals. This graph quantitates the interval distribution of the record.

The heavy line superimposed on the sequential interval histogram in figure 2B is an orthonormal Chebyshev polynomial approximation to the plotted intervals. A linear combination of 6 Chebyshev poly

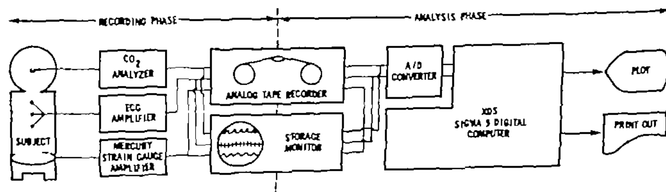


Fig 1 Block diagram of the intensive care monitoring, signal analysis and display systems.

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Keywords Echoencephalography brain tumors, children

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27 CEBOCEPHALY

A Report of Three New Cases

T VALKEAKARI and R. ANTTILA

From the Children Hospital, University of Turku, Turku, Finland

Several forms of faciocerebral malformations may occur varying between cyclopy and normal habitus. One of these malformations is cebocephaly A typical feature of this syndrome is, according to W de Myer a single median nasal aperture and a severe degree of holoprosencephaly It is possible to classify these patients as follows

— phenotype no I cebocephaly with no or only one major extracephalic malformation

— phenotype no II cebocephaly with many extracephalic anomalies and 13—15 trisomy

The clinical picture in the cases with few extracranial anomalies is fairly typical.

— convulsions, which are almost impossible to control with anticonvulsants

— daily temperature fluctuations

— inability to swallow

Bishop et al. reported in 1964 one such case with normal chromosome count and karyotype, but they found an unidentified aminoacid in the cerebrospinal fluid.

Our own material consists of three cases of cebocephaly with no extracranial anomalies. Chromosomes and aminoacids in the cerebrospinal fluid have been examined in two cases and the findings were normal.

Case no 1.

A boy aged 6 months, was born t full term and weighed 3250 g The mother had moderat hypertension during pregnancy Cleft palate and hare lip with single median nasal aperture, flattened bridge of the nose and rudimentary nasal alae were noted at birth. (Fig. 1.) The interorbital distance was 0 9 cm. The child was excited and had small seizures, which were impossible to control with anticonvulsants. The bottoms of the eyes were normal. The plantar reflex was upright and the Moro reflex weak. Transillumination was pathological (Fig. 2.). An EEG showed multiple independent spikes from the anterior parts of hemispheres, from other parts only



Fig. 1.

effective and convenient way of displaying slow variability of the intervals between events in selected segments of long term records.

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26 BRAIN TUMORS IN TWO-DIMENSIONAL ECHO-ENCEPHALOGRAPHY

T VALKEAKARI

From the Children's Hospital, University of Turku, Turku, and the Department of Paediatrics Central Hospital, Kokkola, Finland

Using ultrasound examination the expansive process in the brain can be indirectly noticed in the shift of the normal echoes, primarily the midline echo to the opposite side. *In the direct visualization of tumors,* in addition to the shift or absence of normal echoes, echo complexes of different forms can be seen. In A scan Yukishita et al. (3) *have distinguished type A and type M echoes.* The different form of the echoes is based on different acoustic properties, which are due to different structures of the tumors. Müller et al (1) have presented a method for two-dimensional visualization of brain tumors in A scan.

In B scan type A and type M echoes cannot be seen because the echoes are visualized as bright dots and not as echo deflections. However also in B-scan different tumor-echoes are seen well-delineated and inaccurately delineated ones, homogeneous echoaccumulations and ringformed echoes, and regions completely without echoes, which the absence of normal echoes indicates as pathological (2) Obviously the well-delineated echoes in B-scan correspond to type M echoes in A-scan. The ring formed echo does not for certain indicate that a cyst is in question, but it can also be derived from a tumor which in A scan gives a type M echo An inaccurately delineated, nearly homogeneous accu*mulation in B-scan is received from* the type A tumor in A scan.

Tumor echoes of different types in B-scan are presented as pictures, partly comparing *them to corresponding* A-scan, gammaencephalography and radiological contrast methods.

The advantage of B-scan compared to A scan is the greater probability of detecting a tumor and getting it directly visualized. Besides it is easier in B-scan to follow the variation of the size of the tumor during therapy In B-scan the tumor can also be localized for radiotherapy To estimate the histological structure of the tumor on the basis of B-scan the author's material, however is too small.

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Case no 1.

A boy aged 6 months, was born at full term and weighed 2250 g. The mother had moderate hypertension during pregnancy Cleft palate and hare lip with single median nasal aperture, flattened bridge of the nose and rudimentary nasal alae were noted at birth. (Fig. 1.) The interorbital distance was 0.9 cm. The child was excited and had small seizures, which were impossible to control with anticonvulsants. The bottoms of the eyes were normal. The plantar reflex was upright and the Moro reflex weak. Transillumination was pathological (Fig. 2). An EEG showed multiple independent spikes from the anterior parts of hemispheres, from other parts only



Fig. 1



Fig 2



Fig 3

isoelectrical registration. No chromosomal anomalies were found. Aminoacids in the serum and cerebrospinal fluid were normal. The patient had temperature fluctuations daily between 37.5—39.5 C inability to swallow and excessive mucus production. Bronchopneumonia was the cause of death at the age of 6 months. Autopsy showed typical holoprosencephaly

Case no 2

A girl aged 3 months, was born at full term, weight 3360 g The mother had urinary infections and hypertension during pregnancy The patient had a single median nasal aperture with median lip plate orbital hypotelorism and a flat nose The interorbital distance was 1.2 cm. (Fig. 3) The examination of the eyes showed normal findings except nystagmus. The child had myoclonic seizures immediately after birth and difficulties in swallowing. Unexplained fever between 37.5—38.5 C° was usual. An EEG showed little or no activity except in the anterior parts of the hemispheres. Transillumination was pathological. No chromosomal abnormalities were found. The aminoacids in liquor and in serum were normal. The patient died at the age of 5 months in aspiration pneumonia. Autopsy showed typical holoprosencephaly

Case no 3

A boy aged 5 months, was born at full term and weighed 3080 g. The pregnancy was normal. The child had a single median nasal aperture, cleft and lip palate a flattened bridge of the nose and hypotelorism The interorbital distance was 1 4 cm. From birth the child had cyanosis and respiratory distress with many myoclonic and grand mal seizures daily The temperature varied from 36.2—39.5 C° without any cause. The examination of the eyes was normal except for nystagmus. The child died at the age of 7 months in aspiration pneumonia. Autopsy showed typical holoprosencephaly

SUMMARY

Three cases of cebocephaly with no extracranial anomalies are reported. In two cases chromosomes were examined. The karyotype was found normal in both cases. No abnormal aminoacids in cerebrospinal fluid were detected.

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PREFACE

While the estimation of the sensible water loss (except perspiration) is relatively simple, greatest difficulties are encountered if one attempts an accurate measurement of the "Insensible Water Loss

Whether direct or indirect methods are used for the determination of the insensible water loss, the total amount of water is very close to the basic limitations of the method These limitations are not implied by the methods themselves but by unavoidable conditions such as clothing, bedding, activity of the patient and adsorptions. The object of the investigation, the newborn infant, has to be kept under well-defined, extremely limited conditions, making it unavoidable to deal with a very complex situation.

The technical skill and knowledge necessary to design, build and operate an apparatus of the type described in this presentation exceeds the capabilities of the average physician. There fore, the development requires the collaboration of engineers and/or physicists. Such collaboration corresponds to the general trend in modern medicine, expressed by the development of a new field: biomedical engineering.

The instrumentation is relatively expensive and its operation requires long working hours at least at the beginning of such an investigation.

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Even under favorable conditions it was extremely difficult to treat the problem in the best possible way We think in particular that simultaneously with the water balance the O_2-CO_2 balance should have been registered continuously such a measurement which would give quantitative values for all the terms of the Isenschmid-equation would provide optimal information concerning the water and heat balance of a newborn infant.

Furthermore, it would be desirable to evaluate quantitatively the trace substances (such as ammonium and organic gases) which are lost by the infant, and to register the variations of these losses versus time All this information would be very valuable and of fundamental importance and probably useful for diagnosis. Those investigations could, however not be carried out for lack of personel and financial means.

The problem of the accurate measurement of the insensible water loss of normal newborn infants during the first 24 hours of life is solved. from the medical and technical points of view we consider the present paper which took several years of work, to be completed.

This work awarded the "Clemens von Pirquet Preis 1968" of the Österreichische Gesellschaft für Kinderheilkunde

Ernst Zweymüller
Othmar Preining

Almqvist & Wiksells

BOKTRYCKERI AKTIEBOLAG

UPPSALA 1970

PREFACE

While the estimation of the sensible water loss (except perspiration) is relatively simple, greatest difficulties are encountered if one attempts an accurate measurement of the "Insensible Water Loss

Whether direct or indirect methods are used for the determination of the insensible water loss, the total amount of water is very close to the basic limitations of the method These limitations are not implied by the methods themselves but by unavoidable conditions such as clothing, bedding, activity of the patient and adsorptions. The object of the investigation, the newborn infant, has to be kept under well-defined, extremely limited conditions, making it unavoidable to deal with a very complex situation.

The technical skill and knowledge necessary to design, build and operate an apparatus of the type described in this presentation exceeds the capabilities of the average physician. Therefore, the development requires the collaboration of engineers and/or physicists. Such collaboration corresponds to the general trend in modern medicine, expressed by the development of a new field: biomedical engineering.

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Water is being evaporated continuously from the respiratory tract and the body surface. The evaluation of this so called "Insensible Water Loss" (IW) proved to be very difficult already to early investigators. Hence until now no direct determinations were made. Instead, two procedures have been used.

1. The insensible weight loss (IL) was determined, and the O_2-consumption and CO_2-production were either measured or estimated, and from these data the IW was calculated, or

2. the water loss of the respiratory tract alone, and the water loss through small skin areas was measured, and from this the IW extrapolated (1, 2).

The values of the IW determined in 1929 and 1930 by *Levine et al.* (3, 4) are still considered most reliable for infants and are used to the present day. These authors determined the IL by extremely careful weighing of sleeping infants. They used a specially redesigned balance, one of the scales of which was replaced by a small bed for the infant. The room in which the balance was located was kept at a constant temperature within 1°C, using a heater, window and doors. The relative humidity was also kept constant at ±5% during one experiment. The infants were clothed, the change of weight of the clothes due to room humidity was estimated by determining the change of unused clothes of a similar kind which were kept in the same room during the experiment. With normal infants under basal conditions they found an IL *of 1.0±0.07 g* per hour and kg body weight. All these precautions cannot be considered sufficient. Already Newburgh & Johnston (1) wrote in their paper: "There are many pitfalls in the measurement of IL. Mattresses, bedding and clothing absorb and lose water rapidly when exposed to changing humidities. The common use of wooden bed frames is objectionable since they also absorb and lose water."

Today it is quite clear that the undefined and undefinable water loss or absorption of the different materials, textiles especially may render accurate measurements impossible. Hence it is essential for the measurement of the IW to investigate the hygroscopic properties of all constituent parts of the requisite *equipment* carefully. In any case, comparative experiments, proving the absence of *interfering* hygroscopic properties have to be made. Unfortunately this requirement has not been fulfilled in many publications.

A complete survey of the pertinent literature from 1906 through 1961 contains only 19 papers, of which only 7 deal with children (5). This indicates how little has been done in this essential field, mainly because the basic difficulties are very great. The results of 5 papers (4, 6, 7, 8, 9) are summarized in Table 1. The values reported by Healy et al. (10) and Sturtz et al. (11) were not taken into account since *they concern ill children* only. As no measurements of the IW of the newborn were performed up to date with sufficient accuracy for evaluating the infant's water balance, a parameter of great practical value, the authors designed and built a new apparatus enabling direct, accurate measurements of the IW.

This presentation describes the equipment, its operation, and the results obtained.

METHODS

Principles

In contrast to the methods used so far the insensible water loss of the lung and *of the* total body surface (the IW) has been measured directly in the present study. The newborn infant to be investigated was placed in a specially adapted incubator into which air of controlled, constant and accurately adjustable relative humidity and temperature was supplied at a

List of Figures

List of Tables

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Table 1 *Literature survey of IW values of normal healthy children*

Author Year	No of children (number of measure-ments)	Age	Condition	Method	IW (mg/h, kg body wt.)	Water loss through respiratory tract only (mg/h, kg body wt.)
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Law 1938	46 (86)	8d 11m	Basal	Weighing of the clothed sleeping infant in a special bed	Mean 1 240 Range 686–1 802	—
Hooper et al. 1954	4	d 27d	Basal	Face mask, absorption, weighing of the absorbent	—	Mean 340 Range 270–510
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Ill infants not considered [a] Standard deviation. Age in years.

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Description of apparatus

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The humidifier

The humidifier as well as the heat exchanger were built in our institute and essentially consisted of a rectangular mantle tube the dimensions are given in Fig. 3

During the operation the inner tube was filled with water to about 1/3 of its height a water gauge was used to control the exact level. To increase the surface of the water a linen cloth was fixed on a metal frame Fig. 4 shows the humidifier with this cloth. A Hoeppler Ultrathermostat (Haake, Berlin type F) supplied water of constant temperature to the mantle of the humidifier The same temperature-controlled water was used after it had passed the humidifier in the heat exchanger and was later returned to the thermostat. It is essential that the air after having passed the humidifier should not change its temperature any more In order to ensure this the connecting tube from the humidifier to the incubator was also in the form of a thermostatic temperature-controlled mantle tube It is shown in Fig. 4

Testing the functioning of the humidifier

In a separate preliminary investigation the water intake of the air passing the humidifier at different temperatures was measured with respect to its flow rate, providing a possibility to check the degree of saturation of the air leaving the humidifier under operating conditions. The results are given in Fig. 5 The horizontal parts of the curves correspond to saturation, the descending parts show that at this flow rate saturation is no longer achieved. It is seen from this figure that at a flow rate of 6 l min saturation is achieved at all temperatures employed. This test was made with practically completely dry compressed air and ordinary room air was used for the experiments, it can hence be safely assumed that

Fig 1 Set-up for the direct determination of the insensible water loss of newborn infants, schematically

saturation in the humidifier was achieved at all times.

The incubator

A Draeger incubator (Model II-M-6000) was modified in the following way: the interior had to be sealed completely; for this purpose the balance had to be removed and the resulting opening closed with a brass plate and rubber sealing. The sealing of the heating element was ensured by applying grease to the surfaces. The air intake from the humidifier was also changed by the introduction of further seals. The agitating pump remained unchanged; its air filter was removed to prevent water adsorption. The standard model humidifier was not used, the openings for the water supply were completely sealed. The Lucite hood was first shortened and was later replaced by a removable brass hood. The Lucite and brass hoods were pressed by mechanical means against the rubber seals on the lower part of the incubator. The brass was covered by Styropore to ensure thermal insulation. A glass window at the top

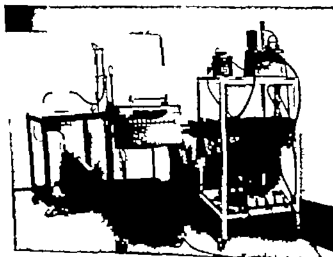


Fig 2 View of the set-up for the direct determination of the insensible water loss of newborn infants.

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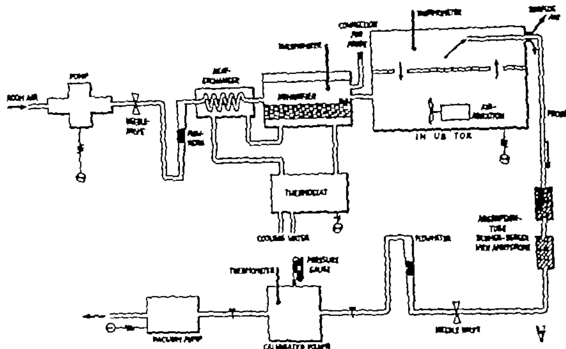


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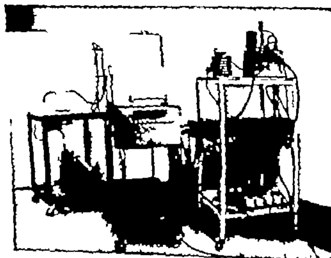


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Table 4 *Weighing record (example)*

Experiment no., 52. Date: 6.10.65

Absorption tube 1 Inlet Outlet	Weight before experiment (g)	Weight after experiment (g)	ΔG (mg)	Absorption tube for control: Absorption tube 2 Inlet Outlet	Weight before experiment (g)	Weight after experiment (g)	ΔG (mg)	Result: Sum ΔG (mg)	Sum ΔG / 2.15 (mg/l)
66–65	24.8869	24.9264	39.5	46–45	28.8529	28.8528	−0.1	39.5	—
15–16	27.0256	27.0646	39.0	70–69	24.4887	24.4887	0.0	39.0	—
36–35	26.8331	26.8720	38.9	41–42	26.9799	26.9798	−0.1	38.9	—
38–37	25.1347	25.1827	48.0	21–22	28.5230	28.5231	0.1	48.1	22.37
130–30	27.4016	27.4500	48.4	19–20	26.7243	26.7241	−0.2	48.4	22.51
67–68	24.2209	24.2704	49.5	74–73	28.0095	28.0095	0.0	49.5	23.02
18–17	26.9653	27.0148	49.5	46–45	28.8528	28.8526	−0.2	49.5	23.02
46–45	24.9405	24.9901	49.6	70–69	24.4887	24.4886	−0.1	49.6	23.07
68–67	28.4504	28.5002	49.8	41–42	26.9798	26.9798	0.0	49.8	23.16
39–40	29.1842	29.2361	51.9	21–22	28.5231	28.5228	−0.3	51.9	24.14
14–13	22.1628	22.2147	51.9	19–20	26.7241	26.7245	0.4	52.3	24.33
18–17	28.4456	28.4841	38.5	74–73	28.0095	28.0096	0.1	38.6	—
66–65	24.9264	24.9653	38.9	46–45	28.8526	28.8529	0.3	39.2	—
15–16	27.0646	27.1027	38.1	70–69	24.4886	24.4895	0.9	39.0	—

culated according to eq. (7) (appendix). The results are given in Fig. 7. The water loss (positive) or intake (negative) during each measuring period is given vs. the measuring time (in measuring periods). From this figure it can be seen that the error is less than 50 mg/kg body weight and hour for a measuring period of 10 min.

A number of blank tests were made throughout the whole series of experiments. From a total of 86 measuring periods of blank tests the standard deviation in mg/kg body weight and hour for a hypothetical 3.00 kg infant was calculated; the result is 59.6 mg/kg body weight and hour.

Accommodation of the infant

(*a*) *The use of diapers.* At first the completely naked infant was put on folded diaper under the assumption that by this method it is least irritated and the cleaning of the incubator tray after urine and meconium discharge is easily possible. However blank tests with diapers showed that they exhibit a large and, due to the different pretreatment, uncontrollable water intake. Therefore diapers proved to be unsuitable. Fig. 8 shows the results of 2 blank tests with diapers (I-25 and I-27). The values which are reduced for a 3.00 kg infant are after period of 50 min still so high that the water intake of one single diaper is of the same order of magnitude as the water loss of the infant.

The influence of diaper used as bedding on the results are also given in Fig. 8 (I-21). The water loss is minimal (compare, for instance with Fig. 15).

(*b*) *Lucite tray.* The newborn was placed on specially designed Lucite tray to avoid soiling of the incubator by urine and meconium. However the Lucite also proved hygroscopic (Fig. 9). In addition, the infants obviously disliked the Lucite tray (indicated by in-

Table 5. *Classification according to the activity record*

Activity record: Sleep, S Awake, W	Intensity of motion	Crying	Activity class
S	0	0	A
S	1	0	
W	0	0	B
W	1	0	
W	2	0	C
W	0	1	
W	1	1	
W	2	1	

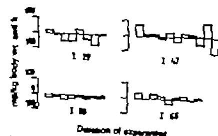


Fig. 7 Blanks. The number of the test is given in the diagram. All tests were evaluated for 3.00 kg infant. Time in periods of 10 min.

Table 2. *Experiment record (example)*

Experiment no 52. Date 6.10.65 Remarks none. Name Misak Sex f Age 16 h. Body weight bef.exp 2 860 g. Body length 48 cm. Body surface 0 185 m Length of remainder of umbilical cord 4.5 cm

		Temperatures							Absorption tube				
									1		2		
Clock time	Time (min)	Room (°C)	Thermostat (°C)	Incubator (°C)	Flask (°C)	r h. room (%)	Barom. pressure (mm/Hg)	Remaining press. flask (mm/Hg)	Inlet	Outlet	Inlet	Outlet	Flow rate through absorption tube (l/min)
8 00	—	—	—	—	—	—	—	—	—	—	—	—	—
8.05	—	21.8	20.8	32.5	21.5	55	744	52	66	65	46	45	0 4[b]
8 14	—	22.0	20.9	32..	20.5	54	744	54	15	16	70	69	0 4[b]
8.22	—	22.1	20.8	32.2	20.9	55	744	54	36	35	41	42	0 4[c]
8.30	0	22.1	20 8	32.1	21 1	55	744	52	38	37	21	22	0 4
8 40	10	22.1	20.9	32.0	21 7	55	744	54	130	30	19	20	0.4
8.50	20	22.2	20 7	32.0	21.3	55	544	54	67	68	74	73	0.4
9.00	30	22.2	20.8	31.9	21.5	55	744	54	18	17	46	45	0.4
9 10	40	22.5	20 7	31.9	21.3	56	744	54	46	45	70	69	0.4
9.20	50	22.2	20.9	31 9	21.5	56	744	54	68	67	41	42	0.4
9 30	60	22.2	20 9	32.1	21.5	56	744	54	39	40	21	22	0.4
9 40	70	22.2	20.9	32.1	21.2	56	744	54	14	13	19	20	0.4
9 48	—	—	—	—	—	—	—	—	—	—	—	—	—[d]
9.55	—	22.2	20.9	—	21.5	57	744	54	18	17	74	73	0 4[b]
10 03	—	22.2	20 8	—	31 8	56	744	52	66	65	46	45	0.4[b]
10 12	—	22.2	20 8	—	21 8	55	744	52	15	16	70	69	0 4[b]

Relative humidity Infant put into incub [b] Humidifier values. Begin exp [d] Vomiting.

was shortened and the internal volume was reduced from 142.5 l to 97 4 l.

At first blank tests were made. For this purpose only the metallic varnished parts of the infant's bed were placed in the incubator The rubber-covered mattress was abandoned from the beginning since its reaction against various relative humidities was considered undefinable. After the incubator had been closed a stabilization period of 30 min was provided. The evaluation of these blank tests was made assuming an infant of 3 00 kg body weight. For this hypothetical infant the water loss (or intake) was cal-

Table 3 *Record of activities (example)*

Experiment no 52. Date 6.10 65

Time	Asleep AS Awake, AW	Intensity of motion[a]	Crying	Remarks
8.30	AS	0	0	
8.35	AS	0	0	
8 40	AS	0	0	
8 45	AS	0	0	
8.50	AS	1	1 briefly	
8.52	AS	0	0	
8.55	AS	0	0	
9 00	AS	0	0	
9 05	AS	0	0	
9 10	AS	0	0	
9 15	AS	0	0	
9.20	AS	0	0	
9.25	AS	0	0	
9.28	AW	2	1	
9.30	AW	2	1	Skin red
9.36	AW	2	1	Water droplets at mouth
9 40	AW	1	0	Heavy vomiting
9 46	AW	–	–	Meconium discharge

Intensity of motion 0 = none 1 = medium 2 = strong.

Table 4 *Weighing record (example)*

Experiment no., 52. Date: 6.10.65

Absorption tube 1 Inlet Outlet	Weight before experiment (g)	Weight after experiment (g)	ΔG (mg)	Absorption tube for control: Absorption tube 2 Inlet Outlet	Weight before experiment (g)	Weight after experiment (g)	ΔG (mg)	Result: Sum ΔG (mg)	Sum ΔG / 2.15 (mg/l)
66–65	24.8849	24.9264	39.5	46–45	28.8529	28.8528	−0.1	39.5	—
15–16	27.0256	27.0646	39 0	70–69	24 4887	24 4887	0.0	39.0	—
36–35	26 8331	26 8720	38.9	41–42	26.9799	26.9798	−0 1	38.9	—
38–37	25.1347	25 1827	48 0	21 22	28.5230	28.5231	0.1	48.1	22.37
130–30	27.4016	27 4500	48.4	19–20	26.7243	26.7241	−0.2	48.4	22.51
67–68	24.2209	24 2704	49.5	74–73	28.0095	28.0095	0 0	49.5	23.02
18–17	26.9653	27.0148	49.5	46–45	28.8528	28.8526	−0.2	49.5	23.02
46–45	24.9405	24.9901	49 6	70–69	24 4887	24 4886	−0 1	49.6	23 07
68–67	28 4504	28.5002	49 8	41–42	26.9798	26.9798	0 0	49.8	23 16
39–40	29 1842	29.2361	51 9	21–22	28.5231	28.5288	−0.3	51 9	24 14
14–13	22.1628	22 2147	51.9	19–20	26.7241	26.7245	0 4	52.3	24.33
18–17	28.4456	28 4841	38.5	74–73	28.0095	28.0096	0.1	38.6	—
66–65	24.9264	24.9653	38.9	46–45	28.8526	28.8529	0 3	39.2	—
15–16	27 0646	27 1027	38.1	70–69	24 4886	24.4895	0.9	39 0	—

culated according to eq. (7) (appendix). The results are given in Fig. 7. The water loss (positive) or intake (negative) during each measuring period is given vs. the measuring time (in measuring periods). From this figure it can be seen that the error is less than 50 mg/kg body weight and hour for a measuring period of 10 min.

A number of blank tests were made throughout the whole series of experiments. From a total of 86 measuring periods of blank tests the standard deviation in mg/kg body weight and hour for hypothetical 3 00 kg infants was calculated; the result is 59 6 mg/kg body weight and hour

Accommodation of th infant

(a) *The use of diapers.* At first the completely naked infant was put on a folded diaper under the assumption that by this method it is least irritated and the cleaning of the incubator tray after urine and meconium discharge is easily possible. However blank tests with diapers showed that they exhibit a large and, due to the different pretreatment, uncontrollable water intake. Therefor diapers proved to be unsuitable. Fig. 8 shows the results of 2 blank tests with diapers (I-21 *a* and I-27 *a*). The values which are reduced for 3 00 kg infant are after period of 30 min still so high that the water intake of one single diaper is of the same order of magnitude as the water loss of the infant.

The influence of diaper used as bedding on the results are also given in Fig. 8 (I-21). The water loss is minimal (compare, for instance, with Fig. 15).

(b) *Lucite tray.* The newborn was placed on a specially designed Lucite tray to avoid soiling of the incubator by urine and meconium. However the Lucite also proved hygroscopic (Fig. 9). In addition, the infants obviously disliked the Lucite tray (indicated by in-

Table 5 *Classification according to the activity record*

Activity record: Sleep S A ake W	Intensity of motion	Crying	Activity class
S	0	0	A
S	1	0	
W	0	0	B
W	1	0	
W	2	0	C
W	0	1	
W	1	1	
W	2	1	

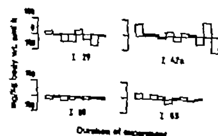


Fig 7 Blanks. The number of the test is given in the diagram. All tests were evaluated for a 3.00 kg infant. Time in periods of 10 min.

Table 2. *Experiment record (example)*

Experiment no 52. Date 6.10 65 Remarks. none. Name Misak. Sex. f Age 16 h. Body weight bef.exp. 2860 g. Body length. 48 cm. Body surface 0.185 m² Length of remainder of umbilical cord 4.5 cm

Clock time	Time (min)	Temperatures: Room (°C)	Thermostat (°C)	Incubator (°C)	Flask (°C)	r h. room (%)	Barom. pressure (mm/Hg)	Remaining press. flask (mm/Hg)	Absorption tube 1 Inlet	1 Outlet	2 Inlet	2 Outlet	Flow rate through absorption tube (l/min)
8 00	—	—	—	—	—	—	—	—	—	—	—	—	—
8 05	—	21.8	20.8	32.5	21.5	55	744	52	66	65	46	45	0.4[b]
8.14	—	22.0	20 9	32.2	20 5	54	744	54	15	16	70	69	0 4[b]
8.2.	—	22.1	20.8	32.2	20.9	55	744	54	36	35	41	42	0.4[b]
8.30	0	22.1	20 8	32.1	21 1	55	744	52	38	37	21	22	0 4[c]
8 40	10	22.1	20.9	32.0	21 7	55	744	54	130	30	19	20	0.4
8.50	20	22.2	20 7	32.0	21.3	55	544	54	67	68	74	73	0.4
9.00	30	22.2	20 8	31.9	21.5	55	744	54	18	17	46	45	0 4
9 10	40	22.5	20.7	31 9	21.3	56	744	54	46	45	70	69	0 4
9.20	50	22.2	20.9	31.9	21.5	56	744	54	68	67	41	42	0.4
9.30	60	22.2	20.9	32.1	21.5	56	744	54	39	40	21	22	0.4
9 40	70	22..	20.9	32.1	21.2	56	744	54	14	13	19	20	0 4
9 48	—	—	—	—	—	—	—	—	—	—	—	—	—[d]
9.55	—	22.2	20.9	—	21.5	57	744	54	18	17	74	73	0.4[b]
10 03	—	2..2	20.8	—	31.8	56	744	52	66	65	46	45	0 4[b]
10 12	—	22.2	20 8	—	21.8	55	744	52	15	16	70	69	0.4[b]

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9 00	AS	0	0	
9 05	AS	0	0	
9 10	AS	0	0	
9 15	AS	0	0	
9.20	AS	0	0	
9.25	AS	0	0	
9.28	AW	2	1	
9.30	AW	2	1	Skin red
9 36	AW	2	1	Water droplets at mouth
9 40	AW	1	0	Heavy vomiting
9 46	AW	–	–	Meconium discharge

Intensity of motion 0 – none 1 – medium 2 – strong.

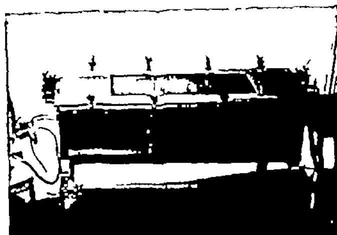


Fig. 12. Incubator model made of sheet brass. Lid with glass window. On the right side the connection to the humidifier, on the left side part of the cart with the absorption tubes is to be seen.

humidity between 48.5 and 55.5% during Series I. The relative humidity of the air in the incubator was higher and not constant during the experiment due to the water production of the infant. The range of this humidities is given for each experiment in Table 7 no. 16. For the Series I it is between 55.5 and 78.5%. Higher humidities led to condensation at the incubator wall (Lucite hood or glass window respectively), since the wall temperature was approximately 3 to 5°C lower than the air temperature in the incubator (mean temperature between incubator and room air: Hey & Mount (27); the room temperature was kept around 24°C, range 20 to 28°C). To increase the range of water loss which can be determined, the relative humidity of the air entering the incubator was somewhat lowered to the range between 37.2 and 45.7% for Series III and IV. The relative humidity of the incubator air was then in the range between 37.6 to 66.9%.

In all cases the environment was such that the infant could be put to sleep relatively easy.

During Series I the Lucite hood was covered with blanket to avoid irritation by illumination, during Series III and IV the brass hood served the same purpose.

Subjects and procedure of testing

The water loss through skin and lungs was determined in a total number of 48 healthy newborn infants before feeding; their ages at the beginning of the test were between 1.3 and 27.3 hours, there were 29 males and 19 females; 28 of them were less, 20 of them more than 12 hours old, delivery had been without complications in all cases.

The investigating procedure was as follows: the infant was cleaned as is usual after delivery, however without applying any protective coating to the skin. After weighing, the naked infant was put into an incubator.

This was necessary to make the infants accustomed to the incubator since otherwise motion and crying would have rendered measurements impossible. If an infant cries for a long period of time, the water loss is so large that condensation occurs on the incubator

Table 6. *Results of the experiments with the model incubator*

Material of lid	Surface treatment of lid	Result
Lucite (5 mm thick)	Washed and dried	Water uptake
Lucite	Petroleum jelly	Water uptake
Lucite	Polished (Funkputz)	Water uptake
Lucite	Silicone oil, applied diluted with ethylene	Water uptake
Lucite	Pure silicone oil, applied concentrated	Water uptake
Brass sheet	Washed and dried	No water uptake
Glass sheet	None	Water uptake
Brass sheet with glass window		
(a) rubber sealing	Window untreated	Water uptake
(b) putty	Window untreated	Water uptake
Brass sheet with Glass window and rubber sealing	Window treated with Acetone-soluble Varnish	No water uptake

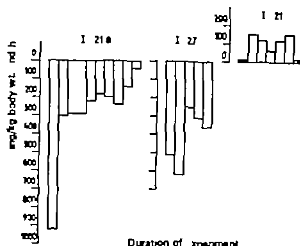


Fig 8 Results of the preliminary tests using diapers. I 21 *a* and I 27 are tests using one diaper each, evaluated for a 3 00 kg infant. Test I 21 was made with a real infant and with a diaper. Time in periods of 10 min.

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Therefore the child was placed directly on the varnished metal sheet usually carrying the mattress.

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Fig. 10 shows the results of an experiment during which 155 ml of urine of a healthy newborn infant, *sealed in a plastic bag, was put into the incubator*. As can be seen the water uptake of the urine through the plastic bag was considerable.

New design of the incubator hood

Some damage on the Lucite hood made a replacement necessary. A new hood was provided by the Draeger Werke in a reduced size. blanks with this new hood yielded the surprising results which are given *in Fig. 11 showing* a considerable water intake of the Lucite.

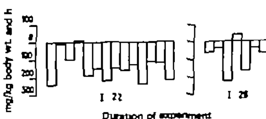


Fig 9 Results of 2 tests using Lucite trays, assuming a 3 00 kg infant. Time in periods of 10 min.



Fig 10 Water intake by urine through a urine sampling bag made of plastic, assuming a 3 00 kg infant. Time in periods of 10 min.

This phenomenon may be explained by the fact that, depending on the conditions of production, Lucite takes *up water per volume and, at the same* time is also permeable for water vapor by diffusion. In addition, sorption layers of water on the Lucite surface, depending on the pretreatment of the surfaces, may occur. Information concerning Lucite, *which chemically is a polymetacryl ester* can be found in the literature (12). The first Lucite hood of the incubator was not hygroscopic, as blank tests had shown (Fig. 7)

To solve the problems of using the right materials in redesigning the incubator hood, a model was built. It was essentially a brass sheet parallelepipid of the size 100×25×25 cm³ which could be fitted with various lids (Fig. 12). Using this model, surfaces and materials which had been *treated in different* ways were tested for their hygroscopicity. The results of these experiments are given in Table 6.

On the basis of these results a new incubator hood was designed, using brass sheets with varnished glass windows sealed with rubber to permit observation of the children. This hood is shown in Fig. 6

Incubator environment

The incubator temperature (see Table 7 no. 8) was kept during each experiment at a level that the infant felt comfortable. Between experiments there was a little variation in the range between 30.5 and 33 6 C.

The air entering the humidifier had a relative

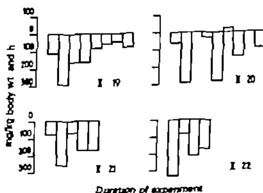


Fig 11 Blank tests with the new Lucite hood assuming a 3 00 kg infant. Time in periods of 10 min.

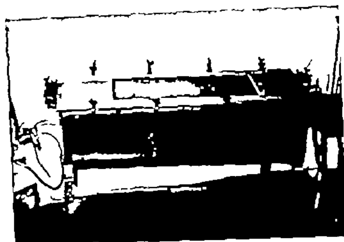


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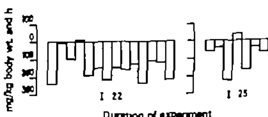


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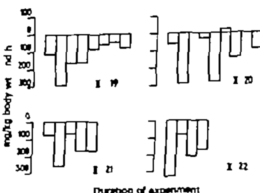


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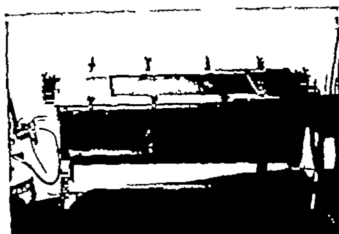


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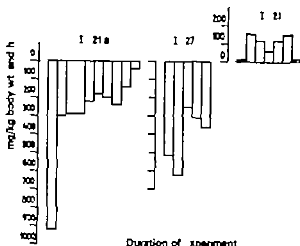


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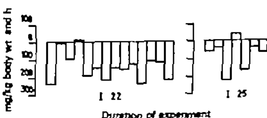


Fig 9 Results of 2 tests using Lucite trays, assuming a 3 00 kg infant. Time in periods of 10 min.

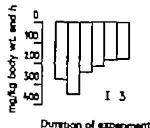


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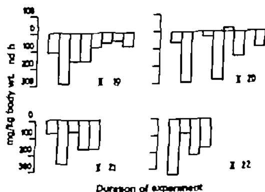


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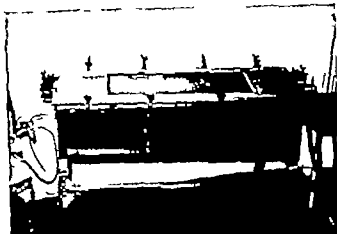


Fig. 12. Incubator model made of sheet brass. Lid with glass window. On the right side the connection to the humidifier, on the left side a part of the cart with the absorption tubes is to be seen.

humidity between 48.5 and 55.5% during Series I. The relative humidity of the air in the incubator was higher and not constant during the experiment due to the water production of the infant. The range of the humidities is given for each experiment in Table 7 no. 16. For the Series I it is between 55.5 and 78.5%. Higher humidities led to condensation at the incubator wall (Lucite hood or glass window respectively), since the wall temperature was approximately 3 to 5°C lower than the air temperature in the incubator (mean temperature between incubator and room air: Hey & Mount (27); the room temperature was kept around 24°C, range 20 to 28 C). To increase the range of water loss which can be determined, the relative humidity of the air entering the incubator was somewhat lowered to the range between 37.2 and 45.7% for Series III and IV. The relative humidity of the incubator air was then in the range between 37.6 to 66.9%.

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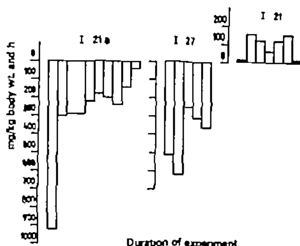


Fig 8 Results of the preliminary tests using diapers. I 21 *a* and I 7 are tests using one diaper each, evaluated for a 3 00 kg infant. Test I 21 was made with a real infant and with a diaper Time in periods of 10 min.

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Fig. 10 shows the results of an experiment during which 155 ml of urine of a healthy newborn infant, sealed in a plastic bag, was put into the incubator As can be seen, the water uptake of the urine through the plastic bag was considerable

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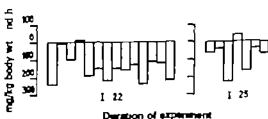


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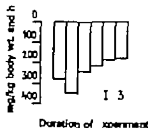


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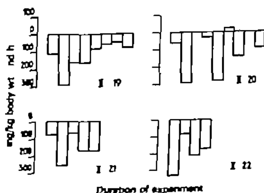


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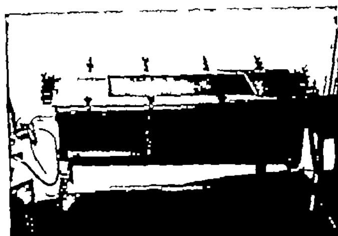


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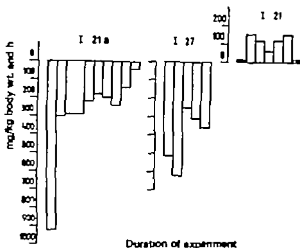


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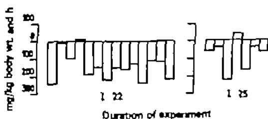


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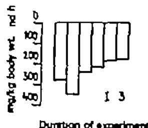


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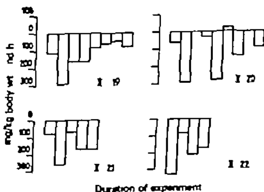


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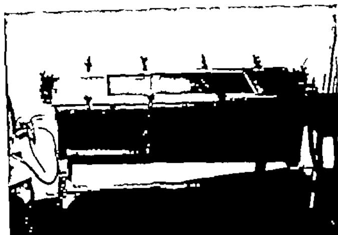


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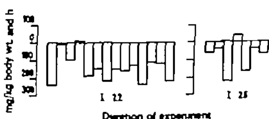


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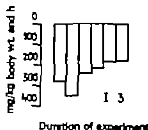


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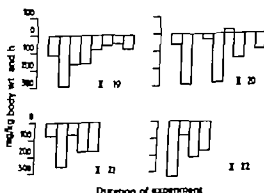


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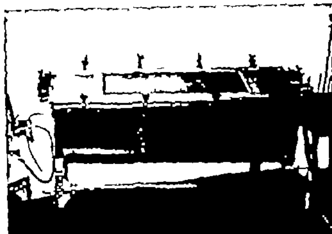


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Table 1 Information on infants and incubator and test results

	Infants						Incubator	
Test no.	Sex, m, f	Age at beginning of test, h	Body weight, kg	Body length, cm	Body surface, m	Length of remainder of umbilical cord, cm	Incubator temperature, C	Water content of air from humidifier mg/l
1	2	3	4	5	6	7	8	9
Series I								
37	f	2.3	3.00	50	0.195	3.5	30.5	18.04
38	f	9 7	2.95	49	0 195	6.5	30.5	17 74
39	m	1.3	3.85	51	0.22	4 0	30.7	17 74
40	m	5.5	2.97	49	0.191	3.0	31.0	18.00
42	m	10.5	3 12	49	0.195	4.5	32.0	18.11
43	m	2.2	3.50	50	0.21	3 0	32.7	17.8
44[e]	f	4 7	4.59	53	0.243	5.0	32.7	17.8
45	f	4 0	3 10	50	0.20	4.5	3_6	17.9
46	f	13.2	4.21	55	0.24	2.5	32.6	17.9
48a	m	8 1	3 40	51	0.22	5.0	32.2	17 67
52	f	17.5	2.86	48	0.185	4.5	32.1	18 14
53	f	21.0	2.70	50	0 185	3.5	32.2	17.81
54	f	5.3	2.30	46	0 165	3.5	3_2	18 19
57	f	2.3	_75	49	0 185	3 0	32.4	18.74
58	m	1 1	2.95	50	0.195	3.5	32.2	18.83
59	f	6.2	2.95	49	0.19	2.5	32.3	18.56
60	m	4 0	4.30	53	0.235	3 0	32.2	18.77
61	m	9 ?	3 65	51	0.215	4 0	32.4	18.51
62	m	7.2	3.30	51	0.205	4 0	32.2	18.28
63[d]	m	3 9	3.82	52	0.225	4.0	32.3	18.33
64_I	f	23.9	2.90	50	0.19	1 0	32.2	18 4
64_{II}	m	27.3	2.92	50	0.195	1.5	32.1	18 4
67	m	16 7	2.90	48	0 185	2.0	32.2	18.51
68	m	15 6	3.29	52	0.21	5.0	32.2	18.33
69	m	17.3	3.20	48	0 195	3 0	3_1	18.33
70	f	14.9	3.38	50	0.205	3.5	32.6	17.86
71	f	9.0	3 46	50	0.21	3 0	32.0	18.05
72	f	13 4	3.20	51	0.205	1.0	3_0	18.56
73	m	9.9	3 10	51	0.20	3	3_1	18 23
74	m	12.7	3 63	5	0.22	4	32.0	18 47
75	m	18.1	3 81	53	0.225	4	32.3	18.26
76	m	14 7	4.57	55	0.25	3	3_5	18.07
Series III								
8	f	10.9	_45	45	0 165	4	33.2	15.99
9	f	9 9	3.29	48	0 195	3	33 6	14.97
18	f	9.3	3_7	50	0.205	5	33 6	14.51
19	m	18 7	3.59	57	0.23	5	33 6	14 60
20	f	9 4	3.25	49	0.20	6.5	33 6	14.37
Series IV								
6	m	17.3	3 85	52	0.225	5	32.2	14 64
7	m	12.1	3.75	52	0.22	6	31 4	14 69
8	m	18.2	3 06	49	0.195	4.5	31 5	14.87
12[e]	f	5 6	2.80	47	0 165	3.0	31.8	15 07
14[f]	m	10 7	3 46	52	0.215	3 0	31.2	14 84
17[g]	m	6.7	3 62	51	0.215	6.0	32.1	15_1
20	m	4 7	3.90	48	0.215	3.5	31 1	14 79
21	m	14.3	3.00	49	0.190	2.5	31 5	15 49
22	f	7 8	3 75	51	0.22	4 0	30.8	15.07
23	m	20.8	3.74	51	0.22	3.5	32.0	14.98
24	m	7.5	3.56	50	0.21	3.5	31 0	15.12

According to J D Crawford, M L. Terry & G M. Rourke (13). [d] Sleep duration ... uring

Bleeding umbilicus. [f] Saliva flow [g] Bleeding umbilicus.

		Results				
Saturation at incubator temperature, mg/l	Relative humidity of air entering the incubator at incubator temperature, %	No. of measuring periods of 10 min. each	Activity during these periods, A, B, C	Mean water loss through skin and lungs/body weight, mg/kg body wt. and h	Mean water loss through skin and lungs/body surface, g/m² and h	Range of relative humidity of the air leaving the incubator %
10	11	12	13	14	15	16
32.5	55.5	4	C	651	10 01	71,3–75,5
		4	A	582	8.95	
32 5	54.6	2	C	600	9.08	68,9–78,5
32 8	54.1	2	C	677	11.85	72,4–77,9
33.4	53.9	1	C	819	12.74	64,0–69 7
35.2	51 4	3	A	471	7.54	59,5–71 7
36.7	48.5	8	C	742	12.37	69,5–73 4
36 7	48.5	3	C	560	10.36	64,6–70,0
		7	A	438	8.27	
36 6	48 9	7	B	666	10.32	64 6–68,5
36 6	48.9	7	B	543	9.53	57,0–70,_
35 6	49 6	8	A	545	8 42	63 1–68,3
33.4	51 2	5	A	530	8.19	63,1–68,7
		2	C	731	11.30	
35.6	50 0	9	A	470	6.86	58,8–62,6
35 6	51 1	2	C	718	10 01	65 4–71 6
		2	B	625	8.71	
36 0	52.1	5	C	674	10.02	65 4–71,3
35 6	52.9	9	A	452	6.84	58,6–64,5
35 8	51.8	2	A	621	9 64	65,5–71,8
35 6	52.7	9	A	375	6.86	67,0–69,2
36 0	51 4	6	A	394	6.69	61,3–65,4
35 6	51.3		A	350	5.63	58,0–60,5
35.8	51.2	8	B	516	8 76	65,3–70,1
35.6	51 7	9	A	597	9 11	59 7 72,7
33.4	52.0	4	C	683	10.23	63,5–68,6
35 6	52 0	8	A	437	6.85	57,9–65,0
35 6	51.5	2	C	449	7.03	66,6–69,9
35 4	51 8	2	B	600	9.85	63,0–67,5
36.6	48.8	12	A	399	6.58	55,5–62,0
35 2	51 3	8	A	461	7.60	62,8–67,2
35.2	52 7	2	A	500	7.80	65,0–66,5
35 4	51.5	2	C	574	8.18	67,0–69,3
		3	C	612	9 49	
35.2	52.5	7	A	489	7.58	69,0–74,8
35.8	51.0	9	C	627	10.35	59,5–63,5
36.2	49 9	4	A	371	6.28	66,0–75,3
		3	C	554	10.13	
37 7	42 4	5	A	480	7 13	52,3–57,0
		2	C	752	11 1	
38.6	38.8	4	A	482	7 16	
38 6	37 6	22	A	372	6.28	47,8–51,8
38 6	37.8	5	A	300	4 78	44,1–46,0
38 6	37_	21	A	338	5.28	44,8–49,9
		9	A	437	7.10	48,5–50 1
35.6	41 1	22	A	404	6.91	51,0–63,3
34.1	43 0	9	A	400	6.82	54,6–60,7
34.3	43.4	4	A	446	.00	51 1–61,6
34 8	43.3	4	A	528	8 96	42,4–54 7
33 6	44 2	9	A	429	6.90	46,8–59,8
35 4	43.0	3	A	441	7 43	46,2 55,0
33.5	44 1	3	C	803	14.57	56 0–65,3
34.3	45.2	1	A	499	7 79	45 4–55,0
33 0	45.7	1	C	427	12.39	39,3–60,5
		2	A	533	9 09	
35.1	42.7	5	C	783	13.31	
33.4	45 3	16	A	412	6.98	43,9–66,2
		4	B	625	10 60	37,6–66,9

⁻riods (100 min) = class O   Blood loss from remainder of umbilical cord.   [e] Highly frequent breathing twins.

Table 7 *Information on infants and incubator and test results*

	Infants						Incubator	
Test no	Sex, m, f	Age at beginning of test, h	Body weight, kg	Body length, cm	Body surface,[a] m²	Length of remainder of umbilical cord, cm	Incubator temperature, C	Water content of air from humidifier mg/l
1	2	3	4	5	6	7	8	9
Series I								
37	f	2.3	3 00	50	0.195	3 5	30.5	18 04
38	f	9 7	2.95	49	0 195	6.5	30.5	17 74
39	m	1.3	3.85	51	0.22	4.0	30.7	17 74
40	m	5.5	2.97	49	0.191	3 0	31.0	18.00
42	m	10.5	3 12	49	0.195	4.5	32.0	18 11
43	m	2.2	3.50	50	0.21	3.0	32.7	17.8
44[e]	f	4 7	4.59	53	0.243	5.0	32.7	17.8
45	f	4 0	3 10	50	0.20	4.5	32.6	17.9
46	f	13.2	4.21	55	0.24	2.5	32.6	17 9
48a	m	8 1	3 40	51	0.22	5 0	32.2	17.67
52	f	17.5	2.86	48	0.185	4 5	32.1	18.14
53	f	21 0	2.70	50	0 185	3.5	32.2	17 81
54	f	5 3	2.30	46	0 165	3.5	3[illegible].2	18 19
57	f	2.3	2.75	49	0.185	3 0	32.4	18 74
58	m	21 1	2.95	50	0.195	3.5	32.2	18.83
59	f	6.2	2.95	49	0 19	2.5	32.3	18.56
60	m	4 0	4.30	53	0.235	3 0	32.2	18.77
61	m	9.2	3 65	51	0.[illegible]15	4 0	32.4	18.51
62	m	7.2	3.30	51	0.205	4 0	32.2	18.28
63[d]	m	3.9	3 82	52	0.225	4.0	32.3	18.33
64_I	f	23.9	2.90	50	0.19	1 0	32.2	18 4
64_{II}	m	27.3	2.92	50	0 195	1.5	32.1	18 4
67	m	16.7	2.90	48	0.185	2.0	32.2	18.51
68	m	15 6	3.29	52	0.21	5.0	32.2	18.33
69	m	17 3	3.20	48	0 195	3.0	32.1	18.33
70	f	14.9	3.38	50	0.205	3.5	32.6	17 86
71	f	9.0	3 46	50	0.21	3.0	32.0	18.05
72	f	13 4	3.20	51	0.205	1 0	32.0	18.56
73	m	9.9	3 10	51	0.20	3	3[illegible]1	18 [illegible]3
74	m	12.7	3 63	52	0.[illegible]2	4	32.0	18 47
75	m	18 1	3 81	53	0.225	4	32.3	18.26
76	m	14 7	4 57	55	0.25	3	32.5	18 07
Series III								
8	f	10 9	2.45	45	0 165	4	33.2	15 99
9	f	9.9	3.29	48	0.195	3	33 6	14.97
18	f	9.3	3.27	50	0.205	5	33 6	14.51
19	m	18 7	3.59	57	0.23	5	33 6	14 60
20	f	9 4	3.25	49	0.20	6.5	33 6	14.37
Series IV								
6	m	17.3	3 85	52	0.225	5	32.2	14 64
7	m	12.1	3 75	52	0.22	6	31 4	14 69
8	m	18.2	3 06	49	0 195	4.5	31.5	14 87
12[e]	f	5 6	2.80	47	0 165	3 0	31 8	15 07
14[f]	m	10 7	3 46	52	0.215	3 0	31 2	14.84
17[g]	m	6.7	3 62	51	0.215	6 0	32.1	15.[illegible]1
20	m	4 7	3.90	48	0.215	3.5	31 1	14 79
21	m	14.3	3 00	49	0.190	2.5	31.5	15 49
22	f	7.8	3 75	51	0.22	4 0	30.8	15.07
23	m	20.8	3 74	51	0.22	3.5	32.0	14.98
24	m	7.5	3.56	50	0.21	3.5	31 0	15.12

[a] According to J D Crawford, M L. Terry & G M Rourke (13).
[b] Sleep duration longer than 10 measuring
[e] Bleeding umbilicus. [f] Saliva flow [g] Bleeding umbilicus.

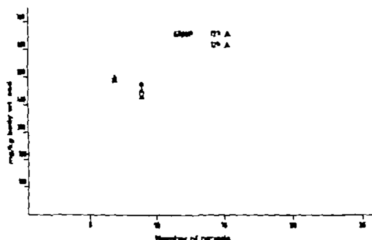


Fig 13 Sleep duration (measuring periods) vs. insensible water loss.

ing to age and sex was therefore only reasonable for class A. The infants of class A were divided into subgroups according to age (above and below the first 12 hours of life) and sex. The results are given in Table 8

Among all infants the male infants older than 1 hours showed a mean water loss which was considerably below that of the other 3 groups therefore, the various classes were reexamined with regard to the class members. In doing so, it was found that each class contained in Table 8 had 1 member who slept particularly long; the male class older than 12 hours, however had 2 such members. The water loss of these long-sleeping members was exceptionally low

Since the infants were examined until crying, urine discharge, or similar effects caused the end of the test, the sleep duration in activity class A is simply given in terms of the number of measuring periods (Table 7) For all the infants the mean water loss vs. sleep duration is given in Fig. 13 This figure shows that the infants sleeping longer than 10 periods have a lower water loss. In addition, the values of the water loss for the 5 long-sleeping infants are very close together

With the infants sleeping less than 10 periods there was no pronounced correlation between the water loss and the sleep duration, which was probably due to the high scattering of the individual values. This high scattering is to a large extent caused by the smaller statistical weight (number of measuring periods) In addition, there could be an influence of the sleep intensity on the water loss. (We think of the possibility of disturbances due to the continuous observation of the infants necessitating illumination, noise, etc., which would be more disturbing the less intense the sleep is.)

Since obviously the long-sleeping infants behave differently they were separated from class A, and were made to form class 0 (in Table 7 this class is indicated by *b*). The remaining infants of class A were called class A Using this new classification Table 8 was recalculated the results are given in Table 9

From Table 9 it can be seen that the mean water loss is essentially independent of age and sex. The values for females older than 12 hours are a little higher which may well be caused by statistical deviation since the group is very small.

With the replacement of the incubator hood the adjustment of the humidifier was changed as well, causing a minor change in the relative humidity in the incubator For the tests of Series I the relative humidity was between 48.5% and 55.5% for Series III and IV between 37.2% and 45 7% (Table 7) These minor changes should, according to the relevant literature, have no influence on the water loss.

Table 8 *Mean water loss of newborn infants of activity class A divided into groups according to age and sex*

Sex	Age (h)	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation	
					mg/kg body wt. and h	%
m	<12	63	9	435	55	12.7
m	>12	80	9	399	45	11.3
f	<12	72	11	437	76	17.4
f	>12	35	4	487	79	16.3

walls. From the room where the infants were kept at the hospital the clothed infants were carried to a room specially adapted for measurements. This room was always kept at constant temperature and was protected from solar radiation. Temperature barometric pressure and relative humidity in the measuring room were registered in intervals of 10 min during the experiment (Table 2)

In the room where the measurements were made the infants were undressed and the length of the remainder of the umbilical cord was measured finally they were put in the measuring incubator After closing the incubator a 30 minutes period was allowed to off set the disturbances during the opening process and to allow the infants to quiet down. Meanwhile the absolute humidity of the air entering the incubator from the humidifier was measured (taking samples from the inner volume of the humidifier through the otherwise closed opening)

Then the measurements started. In intervals of 10 min air samples from the incubator center were taken This was continued until the activity of the infant or the soiling by urine or meconium necessitated an interruption of the test. Finally the absolute humidity of the air from the humidifier was again measured

The difficulties of measurements with newborn infants were great, particularly with regard to the soiling of the incubator by urine and to crying, which made an interruption of the experiment often necessary before useful measurements could be taken.

RESULTS

Table 7 gives the essential information on the newborn infants, on the tests and on the results

First it was considered whether and to what extent the insensible water loss depends upon age and sex A look at the results shows that the influence of the infants activities on the water loss is much greater than the influence of sex and age. Therefore, only infants of approximately equal activity are comparable On the other hand, the evaluation of activities is possible only with low accuracy i.e. one can only differentiate between activity classes. Hence a comparison of the different age and sex groups is only possible under basal conditions.

Even under basal conditions, i e. during sleep or while awake without any motor activities, differences in the water loss have been observed which were caused by differences in breathing behavior By breathing behavior not *only the frequency but also the volume of* breathing, as well as the CO_2–O_2 balance (respiratory quotient) is meant. Since it was not possible to measure the minute volume and the CO_2–O_2 balance, the breathing frequency alone does not specify the breathing behavior and a close analysis of the influence of the breathing behavior was therefore not possible The automatic registration of the breathing frequency and the minute volume is not possible without considerably disturbing the infant. For the registration of the CO_2–O_2 balance rather expensive equipment is necessary

From a total of 48 investigated infants 33 belonged to activity class A, 6 to class B and 19 to class C (some infants belonged to one class for a certain period of time to another later· therefore the total number of class members differs from the number of investigated infants see Table 7) The subdivision accord

For reasons of organization this room was in the same building and on the same floor as the room where the infants were kept during the first part of the measurements during the second part it was in a separate building.

Table 11 *Mean water loss of newborn infants of different activity classes*

Class	No. of measuring periods	No. of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h		Mean water loss (g/m² body surface and h)	Standard deviation g/m² body surface and h	%
O	91	5	390	37	9.5	6.36	0.64	10.0
A	157	28	461	69	14.9	7.47	1.07	14.3
B	30	6	585	61	10.4	9.62	0.72	7.5
C	63	19	670	87	13.0	10.85	1.67	14.4

are completely independent of each other. A comparison of the age groups yields the value $t = 0.53$ for the number $n = 26$, i.e. there is no statistically significant difference between the two groups ($P = 0.05$, $n = 26$, $t = 2.06$).

A comparison of the sex groups yields the value $t = 1.94$ for $n = 26$. This t-value is very close to the value 2.06, which corresponds to a probability value of $P = 0.05$ for $n = 26$. This could be an indication that a minor difference in the IW between the sexes might actually exist.

The comparison given in Table 10 yields the value $t = 1.44$ for $n = 26$. This t-value is so small that it may serve to prove the independence of the measuring results in Series I and III and IV respectively from the differences in humidity.

Finally, an analysis of the significance of the differences between the classes of Table 11 is made (Table 12).

Table 12 proves that the statistical significance of the differences between adjacent activity classes is rather great; therefore, splitting into these four groups has been justified.

For class A, an investigation was made whether the presentation of the results in g/m² body surface and hour or in mg/kg body weight and hour yields smaller standard deviations. Calculations yielded a standard deviation of 14.3% and 14.9% respectively. These differences in the standard deviation are not of statistical significance. The ratio of the standard deviations is 1.04; according to the Fischer F-test this ratio would have to amount to approximately 2 in order to be of statistical significance.

Therefore, both presentations are statistically equivalent; since the body weight is directly measured, the presentation in mg/kg body weight and hour was used.

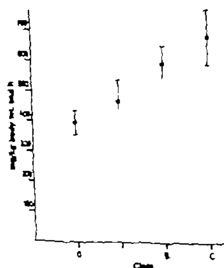


Fig. 14. Relation between water loss of newborn infants and their activity. O mean, I, ± standard deviation.

From tables: 1.93 for $n_1 = 24$ and $n_2 = 27$ with $P = 0.05$. In our case $n_1 = n_2 = 27$.

Table 12. *Significance of the differences between activity classes*

Class 1 for analysis	A	B	C
Class 2 for analysis	O	A	B
t	2.18	4.94	2.14
	31	32	23
t for P 0.05 and given n	2.039	2.037	2.069

Table 9 *Mean water loss of newborn infants of activity class A divided into groups according to age and sex (for comparison the results of class O without subdivision are given)*

Sex	Age (h)	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %
Class A'						
m	< 12	47	8	443	62	14.0
m	> 12	37	7	431	34	7 9
f	< 12	50	10	465	76	16.4
f	> 12	23	3	533	58	10.9
Class O						
—	—	91	5	390	37	9.5

Also this is not to be expected, since according to the paper by Adachi & Ito (14) the water losses through lungs and skin are reciprocal. In spite of this, the result of activity class A of Series I were compared with Series III and IV (Table 10)

This comparison proves that the increase in the relative humidity of the order of 10% does not influence the mean water loss of the infant.

However it is essential for the water loss what type of activity the infant shows Without considering age and sex the average water loss for all infants of one activity class was determined (Table 11) The results are graphically shown in Fig. 14 (See note on p 29)

The systematic increase of the water loss with the activity of the infants could provide a means for quantative evaluation of the activity for a constant environment.

THE STATISTICAL EVALUATION OF THE RESULTS

In comparing the mean values of the IW given in the last paragraph the question arises whether *the differences are of statistical significance*

The analysis with regard to the statistical significance was made using a generalized Student s *t* test (15) The generalization concerns normalized statistical weights for the mean values of the individual infants, as is explained in Appendix, page 27

First Table 9 is investigated more closely Since splitting into 4 subgroups appeared not promising, a comparison was made between 2 subgroups vs. 2 other subgroups, i e all infants of activity class A independent of their sex, younger than 12 hours vs all older infants and all male infants vs the female infants, independent of their age. Such a combination of subgroups is justified if the possible influences

Table 10 *Comparison of mean water loss of class A Series I (higher relative humidities) with Series III and IV (lower relative humidities)*

Series	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt and h	Standard deviation %
I	102	17	473	71	15.0
III and IV	55	11	438	58	13.3

Table 11 *Mean water loss of newborn infants of different activity classes*

Class	No. of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	%	Mean water loss (g/m body surface and h)	Standard deviation g/m² body surface and h	%
O	91	5	390	37	9.5	6.36	0.64	10.0
A	157	28	461	69	14.9	7.47	1.07	14.3
B	30	6	585	61	10.4	9.62	0.72	7.5
C	63	19	670	87	13.0	10.85	1.67	14.4

are completely independent of each other. A comparison of the age groups yields the value $t=0.53$ for the number $n=26$, i.e. there is no statistically significant difference between the two groups ($P=0.05$, $n=26$, $t=2.06$).

A comparison of the sex groups yields the value $t=1.94$ for $n=26$. This t value is very close to the value 2.06, which corresponds to a probability value of $P=0.05$ for $n=26$. This could be an indication that a minor difference in the IW between the sexes might actually exist.

The comparison given in Table 10 yields the value $t=1.44$ for $n=26$. This t-value is so small that it may serve to prove the independence of the measuring results in Series I and III and IV respectively from the differences in humidity.

Finally an analysis of the significance of the differences between the classes of Table 11 is made (Table 12).

Table 12 proves that the statistical significance of the differences between adjacent activity classes is rather great; therefore, splitting into these four groups has been justified.

For class A an investigation was made whether the presentation of the results in g/m² body surface and hour or in mg/kg body weight and hour yields smaller standard deviations. Calculations yielded a standard deviation of 14.3% and 14.9% respectively. These differences in the standard deviation are not of statistical significance. The ratio of the standard deviations is 1.04; according to the Fischer F-test this ratio would have to amount to approximately 2 in order to be of statistical significance.[1]

Therefore, both presentations are statistically equivalent, since the body weight is directly measured, the presentation in mg/kg body weight and hour was used.

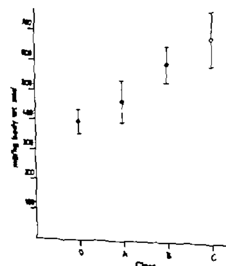


Fig. 14. Relation between water loss of newborn infants and their activity. ○ mean, I, ± standard deviation.

[1] From tables: 1.93 for $n_1=24$ and $n_2=27$ with $P=0.05$. In our case $n_1=n_2=27$.

Table 12. *Significance of the differences between activity classes*

Class I for analysis	A	B	C
Class II for analysis	O	A	B
t	2.18	4.94	4.14
	31	32	23
t for P 0.05 and given	2.039	2.037	2.069

Table 9 *Mean water loss of newborn infants of activity class A divided into groups according to age and sex (for comparison the results of class O without subdivision are given)*

Sex	Age (h)	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %
Class A						
m	< 12	47	8	443	62	14 0
m	> 12	37	7	431	34	7.9
f	< 12	50	10	465	76	16.4
f	> 12	23	3	533	58	10.9
Class O						
—	—	91	5	390	37	9.5

Also this is not to be expected, since, according to the paper by Adachi & Ito (14) the water losses through lungs and skin are reciprocal. In spite of this, the result of activity class A of Series I were compared with Series III and IV (Table 10)

This comparison proves that the increase in the relative humidity of the order of 10% does not influence the mean water loss of the infant.

However it is essential for the water loss what type of activity the infant shows Without considering age and sex the average water loss for all infants of one activity class was determined (Table 11) The results are graphically shown in Fig. 14 (See note on p 29)

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Series	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %
I	102	17	473	71	15.0
III and IV	55	11	438	58	13.3

Table 11 *Mean water loss of newborn infants of different activity classes*

Class	No. of measuring periods	No. of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %	Mean water loss (g/m² body surface and h)	Standard deviation g/m² body surface and h	Standard deviation %
O	91	5	390	37	9.5	6.36	0.64	10.0
A	157	28	461	69	14.9	7.47	1.07	14.3
B	30	6	585	61	10.4	9.62	0.72	7.5
C	63	19	670	87	13.0	10.85	1.67	14.4

are completely independent of each other. A comparison of the age groups yields the value $t=0.53$ for the number $n=26$, i.e. there is no statistically significant difference between the two groups ($P=0.05$, $n=26$, $t=2.06$).

A comparison of the sex groups yields the value $t=1.94$ for $n=26$. This t value is very close to the value 2.06, which corresponds to a probability value of $P=0.05$ for $n=26$. This could be an indication that a minor difference in the IW between the sexes might actually exist.

The comparison given in Table 10 yields the value $t=1.44$ for $n=26$. This t value is so *small* that it may serve to prove the independence of the measuring results in Series I and III and IV respectively from the differences in humidity.

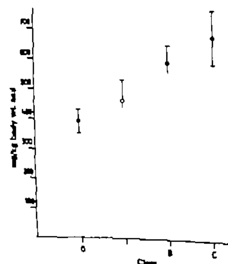


Fig. 14. Relation between water loss of newborn infants and their activity. O mean; I standard deviation.

Finally an analysis of the significance of the differences between the classes of Table 11 is made (Table 12).

Table 12 proves that the statistical significance of the differences between adjacent activity classes is rather great, therefore, splitting into these four groups has been justified.

For class A an investigation was made whether the presentation of the results in g/m² body surface and hour or in mg/kg body weight and hour yields smaller standard deviations. Calculations yielded a standard deviation of 14.3% and 14.9% respectively. These differences in the standard deviation are not of statistical significance. The ratio of the standard deviations is 1.04; according to the Fischer F-test this ratio would have to amount to approximately 2 in order to be of statistical significance.

Therefore, both presentations are statistically equivalent; since the body weight is directly measured, the presentation in mg/kg body weight and hour was used.

From tables: 1.93 for $n_1=24$ and $n_2=27$ with $P=0.05$. In our case $n_1=n_2=27$.

Table 12. *Significance of the differences between activity classes*

Class 1 for analysis	A	B	C
Class 2 for analysis	O	A	B
t	2.18	4.94	4.14
	31	32	23
t for P 0.05 and given	2.039	2.037	2.069

Table 9 *Mean water loss of newborn infants of activity class A divided into groups according to age and sex (for comparison the results of class O without subdivision are given)*

Sex	Age (h)	No of measuring periods	No of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %
Class A						
m	<12	47	8	443	62	14 0
m	>12	37	7	431	34	7.9
f	<12	50	10	465	76	16.4
f	>12	23	3	533	58	10.9
Class O						
—	—	91	5	390	37	9.5

Also this is not to be expected, since according to the paper by Adachi & Ito (14) the *water losses through lungs and skin are reciprocal* In spite of this, the result of activity class A of Series I were compared with Series III and IV (Table 10)

This comparison proves that the increase in the relative humidity of the order of 10% does not influence the mean water loss of the infant

However it is essential for the water loss what type of activity the infant shows. Without considering age and sex the average water loss for all infants of one activity class was determined (Table 11) The results are graphically shown in Fig. 14 (See note on p 29)

The systematic increase of the water loss with the activity of the infants could provide a means for quantative evaluation of the activity for a constant environment.

THE STATISTICAL EVALUATION OF THE RESULTS

In comparing the mean values of the IW given in the last paragraph the question arises whether the differences are of statistical significance

The analysis with regard to the statistical significance was made using a generalized Student's *t*-test (15) The generalization concerns normalized statistical weights for the mean values of the individual infants, as is explained in Appendix, page 27

First Table 9 is investigated more closely Since splitting into 4 subgroups appeared not promising, a comparison was made between 2 subgroups vs 2 other subgroups, i.e all infants of activity class A independent of their sex, younger than 12 hours vs. all older infants and all male infants vs the female infants, independent of their age Such a combination of subgroups is justified if the possible influences

Table 10 *Comparison of mean water loss of class A Series I (higher relative humidities) with Series III and IV (lower relative humidities)*

Series	No of measuring periods	No. of infants	Mean water loss (mg/kg body wt. and h)	Standard deviation mg/kg body wt. and h	Standard deviation %
I	102	17	473	71	15 0
III and IV	55	11	438	58	13.3

with different infants of the same author is caused by the considerable inaccuracy of the experimental measurements rather than by physiological variations, since the data refer to basal conditions. However it must be noted that the IW and thus also the IL might depend on the environmental factors. The conditions for our experiments were chosen in such a way as to make the naked infants feel well, i.e. to put most of them to sleep In all experiments the incubator temperature was between 30.5 and 33.6 C, while the relative humidity ranged from 37.2 to 55.5 % (Table 7 no. 11) In addition, the air in the incubator was intensively agitated. A greater deviation from these conditions could certainly explain deviations from the values (1 5) This is also indicated by the very small differences of the IW between the five infants of activity class O

Intensity of sleep and IW

A comparison between activity classes O and A indicates that the differences of the IW between the groups are caused at least partly by differences in sleep intensity For all investigations during sleep it is essential to determine the type of sleep The two types distinguished are type I and II, type I being the quiet sleep which shows particularly low breathing frequency in contrast to type II (18). It is very likely therefore, that the long-sleeping infants of class O belonged to type I as opposed to most infants of class A who belonged to type II.

Variation of the IW of sleeping infants over a certain period of time

An examination of the various measuring values of infants of class O shows that single values or groups of values may deviate considerably from the mean values (Fig. 15) It is very likely that these deviations are real and represent a change of the IW during sleep. Similar observations were made by Day (18), who distinguished classes of infants according to the different behavior of their IL vs. time during sleep.

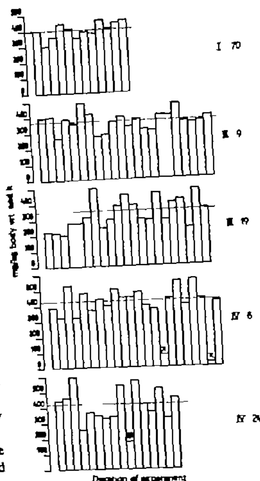


Fig 15 IW vs. time, for the infants of activity class O Time in periods of 10 mm. The abnormally low values marked by and O are due to errors; caused by improper handling of one absorption tube and O by weighing errors, as the re-examination of the records showed.

Activity and IW

The IW of an active infant is considerably raised, the activity class C shows an IW higher by a factor of approximately 1 7 Crying of the infant for a longer period of time can be expected to raise the IW by a factor larger than 2, if compared with basal conditions. Such infants could not be investigated with our equipment, since condensation occurred in the incubator and rendered measurements impossible if the IW became too large. Therefore the mean value of the IW for activity class C must be considered to be a minimum value An ex

Table 13 *Values of O_2, CO_2 and RQ for five infants according to Cross et al*

No	Age (days)	Sex	Birth weight (kg)	O_2-consumption (ml)[a]	CO_2-production (ml)[a]	RQ
18	0 50	f	3 70	368	266	0 72
24	0 19	m	3 97	339	292	0 85
27	0 19	m	3 80	297	280	0.94
27	0.36		3.80	370	297	0.80
29	0 42	m	3.5	4.5	302	0 72

[a] Calculated per kg body weight and hour at 0°C and 760 mm Hg.

DISCUSSION OF THE RESULTS

The Isenschmid-equation

For a comparison of the directly measured values of the IW and of the IL values given in the literature it is necessary to discuss the relation between these quantities This relation is given by the Isenschmid-equation (16) It connects IW and IL, taking into consideration the weight difference between oxygen intake and carbon dioxide loss For

IL = Insensible weight loss in g
IW = Insensible water loss in g
O = Oxygen intake in g
CO_2 = Carbon dioxide loss in g

it appears in the following form

$$IL = IW + CO_2 - O_2$$

Of these quantities only IW needs a detailed discussion.

The definition of the IW

In accordance with Kuno (2) IW designates the total water loss of the respiratory tract and the body surface in the vapor phase Sweat glands contribute very little to this water loss, even if sweat drops are occasionally visible on the skin (it is true that extremely small sweat droplets are visible on some regions of the skin during insensible perspiration. It cannot therefore be denied categorically that some sweat glands are active continuously But such a tonic secretion of sweat is so little in amount as to have practically no significance in the rate of insensible perspiration" (14)) A strong sweat secretion is, however not considered to be part of the IW

Table 14 *Calculation of the IL for activity classes O and A*

Class	$IW + CO_2 - O_2 = IL$
O	390 + 569 − 513 = 446
A	461 + 569 − 513 = 517

All values in mg/kg body wt. and h.

The respiratory quotient

For an evaluation of the Isenschmid-equation it is necessary to know the values of O and CO_2 Cross et al (17) measured CO and O_2 values in five healthy newborn infants younger than 24 hours They also calculated the respiratory quotient for these infants, namely

$$RQ = \frac{CO_2 \text{ in mol.}}{O_2 \text{ in mol}}$$

Their results are given in Table 13 They yield a mean O_2 intake of 358 ml/kg body weight and hour which corresponds to 513 mg/kg body weight and hour and a mean CO_2 loss of 287 ml/kg body weight and hour which corresponds to 569 mg/kg body weight and hour and a mean RQ of 0 81

The determination of the IL

Using these values and our values of the IW for the activity classes O and A a direct calculation of the IL is possible, as shown in Table 14 These results come closely within the range of values of the IL determined by Bruck (5) from the total available literature, i e a range of IL values from 400 to 900 mg/kg body weight and hour Our values are in the lower range and thus are far below the value of Levine et al (4) which is 1 0 g/kg of body weight and hour

Discussion of the IL

We agree with Bruck (5) in that the difference between the results of the different authors or

with different infants of the same author is caused by the considerable inaccuracy of the experimental measurements rather than by physiological variations, since the data refer to basal conditions. However it must be noted that the IW and thus also the IL might depend on the environmental factors. The conditions for our experiments were chosen in such a way as to make the naked infants feel well, i.e. to put most of them to sleep In all experiments the incubator temperature was between 30.5 and 33.6 C, while the relative humidity ranged from 37.2 to 55.5 % (Table 7 no. 11) In addition, the air in the incubator was intensively agitated. A greater deviation from these conditions could certainly explain deviations from the values (1 5) This is also indicated by the very small differences of the IW between the five infants of activity class O

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Variation of the IW of sleeping infants over a certain period of time

An examination of the various measuring values of infants of class O shows that single values or groups of values may deviate considerably from the mean values (Fig. 15) It is very likely that these deviations are real and represent a change of the IW during sleep Similar observations were made by Day (18), who distinguished classes of infants according to the different behavior of their IL vs. time during sleep.

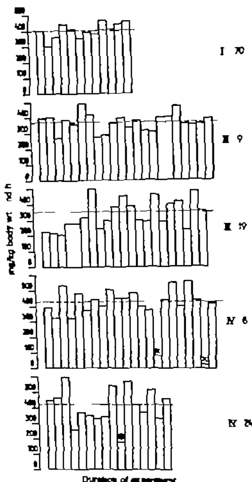


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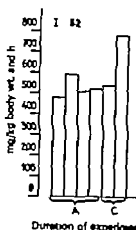


Fig 16 Change of the IW of newborn infants during transition from *sleep to crying. Time in periods* of 10 min.

ample for this increase of the IW in the same infant when changing from sleep to crying is shown in Fig. 16

The heat loss through the IW

The water leaving the body in the form of the IW has to change from the liquid to the vapour phase at body temperature This means that for each gram of water a heat of 0.58 calories is necessary i.e per kg body weight and hour the infants lose an amount of heat through the IW as shown in Table 15

Table 15 *Heat loss of infants of different activity classes through the IW*

Class	Heat (Cal./kg body wt and h)
O	0.226
A	0.[illegible]67
B	0.339
C	0 388

Table 16 *Total heat production of the infants of Table 13*

No	Cal./ kg body wt. and 24 h	Cal./ kg body wt and h
18	41.5	1 73
24	40.1	1 67
27	39.8	1 66
27	42.6	1 78
29	47.3	1 96

The heat balance of newborn infants

For the five infants of the quoted paper Cross also calculated the total heat production under reasonable assumptions[1] concerning the heat production due to the amount of oxygen consumed (Table 16) A mean value of 1 76 calories/body weight and hour was determined for the sleeping infant, i.e. 13 to 15% of the heat produced in the body is lost through the IW

According to investigations of Levine & Marples (20) as well as Newburgh et al (21) the heat loss through the IW amounts to 25% independently of the age This difference from our values may have various causes.

1 newborn infants actually have a lower percentage of heat loss through the IW than older infants, children and adults.

2 The estimate of Cross et al. as to the heat production in newborn infants is too high.

3 Naked infants in an incubator with intensive agitation of the air lose more heat, due to the air convection.

It is impossible to distinguish between these tentative explanations without carrying out further experiments [2]

CONCLUSIONS

(a) Water supply during the first 24 hours of life

The water loss during the first 24 hours of life is in our opinion of great practical importance.

Cross et al. (17) used tables based on Zuntz, N and Schumburg, W A. E. F Studien zu einer Physiologie des Menschen. A. Hirschwald, Berlin, 1901

Very recently the present paper already being in press, Hey E. N and Katz, G (Arch. Dis. Child., 45 1970, 328 The Optimum Thermal Environment for Naked Babies) found for healthy babies during the first weeks of life that "basal evaporative heat loss ccounted for as much as 30 of minimum heat production in a neutral thermal environment if the air was 25% saturated, whereas it accounted for only 19% of minimum heat production when the air was 75% saturated" For similar saturation (see Table 7 no 16) the latter value is in good agreement with our results. However our infants were very likely at temperatures below the neutral thermal environment, which is probably the cause of our somewhat lower values.

Assuming that during the first 24 hours a newborn infant sleeps very quietly for 10 hours (class O), with interruptions also 10 hours (A') and cries for 4 hours (C), a mean IW of 0.5 mg/kg body weight and hour results

Since the total body water of the newborn infant is around 79% of the total body weight, the loss in form of the perspiratio insensibilis is 0.063% per hour or 1.5% for the first day of life with regard to the total body water The mean water loss of the newborn infants by urine discharge during the first day is 0.25 g/kg body weight and hour (22) i.e. only half of the IW-value Since we must except a certain water loss by meconium discharge, the total loss during the first day of life is between -3% of the total body water For very active and crying infants this value is considerably higher This forces us to raise the question whether or not liquid should be supplied to the newborn in any case during the first 24 hours.

(b) Relative humidity and thermal stress

The thermal stress by IW for newborn infants under basal conditions should also be considered. Silverman & Blanc (13) have demonstrated as early as 1957 that with prematurely born infants the rate of mortality can be reduced significantly at the same incubator temperature if the humidity of the air is increased. At the high humidity of 80–90% a mortality rate of 43% was found, while it was 58% at the low humidity of 30–40% In further papers by Silverman et al. (24 25) it was demonstrated that the influence of the humidity on the mortality rate is caused by the thermal stress due to the heat loss via IW The heat loss due to IW at low relative humidities can be compensated by infra-red radiation. If the changes in humidity are counteracted by infra-red radiation of the correct amount, they show no influence on the mortality rate However the increase in relative humidity is much simpler than radiation at the right dose.

For the purpose of practical application this means that the temperature and the relative humidity in the incubator cannot be chosen independently if the environment of the prematurely born or newborn infants is to be made as suitable as possible.

(c) Importance of activity

The motor activity causing an increase in the IW has not been considered in our investigations However it is necessary to measure quantitatively the CO_2–O_2-balance in order to be able to take into consideration the influence of activity In any case increased motor activity (crying) in a dry atmosphere causes a high loss of body water and heat, which should be avoided for newborn and particularly for ill infants. This can be done in 2 ways

1 increased supply of liquid which only replaces the lost water but not the heat

2. placing the infant in an environment where water and heat losses are small, i.e in an incubator with a highly humid atmosphere at the appropriate temperature

(d) Thermal stress and IW

It would be of great interest to study the various influences on the IW i e to investigate situations which do not correspond *to basal* conditions. Among other factors the IW is most *important* for the temperature regulation of the organism. Therefore a highly interesting question would be to what extent it is possible for the newborn infant to adjust the IW to the thermal stress. Such investigations are very important since the *thermal* stress in an incubator is not simply given by the air temperature, but *also by the* radiation exchange with the incubator wall. At low relative humidities the heat loss by evaporation and radiation could increase the thermal stress above a permissible level in spite of the fact that the temperature of the incubator air is relatively high.

(e) Oxygen supply and IW

Since the heat production is also dependent on the O_2-supply the connection between the latter and the IW should be investigated. It is of particular interest how long a newborn infant can compensate the heat loss due to the

low humidity of the environment by increased O_2-consumption, possibly due to a higher O_2-supply

(f) IW and age

The development of the IW according to the age of the newborn infant is an important question Also the amount and type of food administered is to be considered in this respect In a brief preliminary experiment a few infants of the age of 6 days were investigated and were found to show no change in the IW value under basal conditions. In addition we did not find any dependence on the amount and type of food, however the number of investigated infants was too small to yield significant results.[1]

(g) The Isenschmid-equation and trace substances

During the last decade it became possible to measure trace substances in gases at very low concentrations (far below 1 1 000 000) Therefore it would be possible to carry out experiments to investigate other gases besides water and CO which are lost by the organism through lungs and skin The loss of hydrogen and methane (26) is well known but also other gases are lost as occasionally even the rather insensitive human nose registers For this reason the Isenschmid-equation should have a supplemental term, which would certainly not contribute to the weight. However the investigation into the losses of trace substances could be helpful for diagnosis.

If with the air supply trace substances (pollutions) enter the organism, it is very likely that the organism takes them up to a large extent (consider trace concentrations of carbon monoxide) Therefore the air used in the incubator should be precleaned, particularly in large cities where toxic trace substances are always present in the air The plain air intake from the room as it is in use in most hospitals today should certainly be avoided

[1] Investigations with infants of the age of 6 days in an incubator are very difficult because infants of this age who are not normally kept in incubators are greatly disturbed by the change in environment.

SUMMARY

The insensible water loss through the lungs and the body surface of newborn infants has been measured for the first time directly A total of 343 single measurements with 48 newborn infants of both sexes, younger than 28 hours, was performed. The significances of the results were statistically evaluated.

Of our findings the following are the most important.

1 The insensible water loss under basal conditions is between 390–460 mg/kg body weight and hour (mean values of classes O and A') or between 6 36–7 47 g/m² body surface and hour (environment. temp 30.5–33 8 C rel. humidity 37 2–55 5 %)

2. During the first 24 hours of life the water loss is independent of the age

3 There has only been a slight indication that there is a difference between sexes in this age group the values for females are a little higher but this is on the border of being significant.

4 The mode of sleep is of great influence on the insensible water loss. On the average, long-sleeping infants lose much less water than short sleeping infants.

5 The insensible water loss greatly increases with increasing activity of the infant. So far it has only been suspected that there is such an increase, however the increase was never quantitatively determined This increase is, according to our measurements, at least given by a factor of 1 7 it is very likely that with infants who cry intensively this increase is considerably larger

ACKNOWLEDGEMENTS

This work was made possible by the generous support of the Draeger Werk, Luebeck, who supported the work with an incubator model II M 6000 and an analytical balance. They permitted changes on the incubator to be made in our shop and a special incubator hood was produced by them according to our requirements They supported this investigation in

many ways and finally even financed its publication.

We also thank the Milupa company for a financial contribution.

We would like to thank Prof. Dr H Husslein, head of the II. Universitaets Frauenklinik and Prof. Dr E. Gitsch, for support and permission to use their facilities.

APPENDIX

Theory of Evaluation

List of symbols.

V = Volume of the incubator in liters

t = Measuring time in minutes

k = Flow rate of the air entering and leaving the incubator in l/min

C = Water content of the air entering the incubator in mg/l

C_0 = Water content of the air in the incubator at the time $t = 0$ in mg/l

C_t = Water content of the air in the incubator at the time t in mg/l

q = Water loss of the newborn infant or any other object in the incubator in mg/min (negative sign means water intake of the object)

$\bar{q}$ = Mean water loss of the newborn infant during measuring period (in the majority of cases 10 min)

The basic assumption which had to be made to allow for the calculation of the water loss was that the relative humidity throughout the incubator is uniform. This assumption was justified since the incubator air was rapidly circulated by a special pump system, thus facilitating the mixing.

In the differential time interval dt the water content of the incubator air changes by dC_t; the water content of the whole incubator therefore by $V\,dC_t$. During the time dt the amount of water of $k\,C\,dt$ enters the incubator with the inflowing air; in the same time differential the amount of water of $k\,C_t\,dt$ leaves the incubator with the discharged air. In this time differential the newborn (or any other object, for instance diapers) produces the amount of water $q\,dt$. Since no other water source or sink exists, the balance yields the following differential equation.

$$V\,dC_t = [k(C - C_t) + q]\,dt \tag{1}$$

Here V, k and C are constant, C_t is measured as an average over time intervals of approximately 6 min, the quantity q has to be calculated.

The differential equation is easily solved by separation of the variables: from eq. (1) follows

$$\frac{dC_t}{C_t - C - \frac{q}{k}} = -\frac{k}{V}dt \tag{2}$$

Integration of eq. (1) yields

$$\ln\left(C_t - C - \frac{q}{k}\right) = -\frac{k}{V}t + K \tag{3}$$

The integration constant K is determined by using the initial conditions $C_t = C_0$ at the time $t = 0$, therefore

$$K = \ln\left(C_0 - C - \frac{q}{k}\right) \tag{4}$$

Eqs. (3) and (4) yield

$$\frac{C_t - C - \frac{q}{k}}{C_0 - C - \frac{q}{k}} = e^{-(k/V)t} \tag{5}$$

From eq. (5) the water loss q can be calculated algebraically

$$q = k\,\frac{C_t - C(1 - e^{-(k/V)t}) - C_0 e^{-(k/V)t}}{1 - e^{-(k/V)t}} \tag{6}$$

If the value of $C_t = C_{\Delta t}$ (as mean value of approximately 6 min) is measured after a time interval of $t = \Delta t$ (mostly 10 min), the mean water loss $\bar{q}$ can be calculated for the time interval Δt:

$$\bar{q} = k\,\frac{C_{\Delta t} - C(1 - e^{-(k/V)\Delta t}) - C_0 e^{-(k/V)\Delta t}}{1 - e^{-(k/V)\Delta t}} \tag{7}$$

Every 10 min the values of $C_{\Delta t}$ were measured, each pair of consecutive values of $C_{\Delta t}$ permits the calculation of one value of $\bar{q}$, since $C_{\Delta t}$ of

low humidity of the environment by increased O_2-consumption, possibly due to a higher O_2-supply

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of their mean values the t values were calculated according to equation

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s} \frac{n_1 n_2}{n_1 + n_2} \qquad (12)$$

s being the mean standard deviation as defined by eq. (13):

$$s^2 = \frac{(n_1 - 1)\sigma_1^{*2} + (n_2 - 1)\sigma_2^{*2}}{n_1 + n_2 - 2} \qquad (13)$$

The number of degrees of freedom n is given by

$$n = n_1 + n_2 - 2 \qquad (14)$$

Note: After finishing this work measurements of the I.W. of newborn infants were published (Hey E. N. and Katz G., Evaporative water loss in the new-born baby. J. Physiol., 200: 605, 1969).

They used a method very similar to our's and found on premature and full-term infants less than 2 days old an I.W. of 7.86±1.26 g/m² and h (their page 609), which compares well to our value for activity group A of 7.46±1.07 g/m² and h (Table 11). They too mention the strong dependence of I.W. on the activity of the infant (page 610) but they did not investigate into this problem quantitatively.

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Table 17 *Evaluation (example)*

Experiment no 52 Date 6.10 65
Constants $C = 18\ 14$ mg/l $k/V = 0\ 01514$ l/min $k = 5\ 0$ l/min body wt. = _86 kg; $V = 97\ 4$ l

Clock time	Time (min)	Δt (min)	$e^{-(k/V)\Delta t}$	$1-e^{-(k/V)\Delta t}$	$C\Delta t$ (mg/l)	C (mg/l)	C (5) (mg/l)	(7) (4) (mg/l)	(8)+(9) (mg/l)	(6)−(10) (mg/l)	(11) (5) (mg/l)	$q = k$ (1) (mg/l)	(13) 60 / body wt. kg (mg/kg body wt. and h)
1	_	3	4	5	6	7	8	9	10	11	1?	13	14
8.30	0	—	—	—	22.37	—	—	—	—	—	—	—	—
8 40	10	10	0 598	0 40_	22.51	22.37	7.29	13.38	20 67	1.84	4.56	2_8	480
8.50	20	10	0.598	0 40?	23.0?	_2.51	7.29	13 46	20.75	2.27	5 65	28.2	59
9 00	30	10	0.598	0 402	23.0?	23 02	7.29	13 77	?1 06	1 96	4 87	24 4	511
9 10	40	10	0.598	0 40_	23 07	23 02	7.29	13 77	21 06	_01	5 00	25 0	5 4
9.20	50	10	0 598	0 40	23 16	23 07	7.29	13 80	21 09	2.07	5 15	_5 7	540
9.30	60	10	0.598	0 402	?4 14	23 16	7.29	13 85	21 14	3 00	7 47	37 4	783
9 40	70	10	0.598	0 40?	24.33	24 14	7.29	14 44	1 73	_60	6 46	3_4	678

the previous measuring interval can be used as C_0 of the following measuring interval Since for the calculation of $\bar{q}$ pairs of values of $C_{\Delta t}$ are needed from a number of measurements only a number of $\bar{q}$ values reduced by 1 can be obtained The calculation procedure of $\bar{q}$ values is given in Table 17

Method of statistical evaluation

For the evaluation a generalized Student's t test was used

In the following, each variable is characterized by up to 3 indices The first indicating the group the infant belongs to, the second indicating the number of the infant in the group and the third indicating the number of the measuring period

- x_{ijk} – Single value resulting directly from the measurement, period k measured with infant j of group i
- f_{ij} – Number of measuring periods with infant j of group i
- x_{ij} – Mean value over all f_{ij}-measuring periods with infant j of group i
- n_i – Number of infants of group i
- x_i – Mean value over all measuring periods of all infants of group i
- N_i – Number of measuring values in group i
- $N_i = \sum_j f_{ij}$
- g_{ij} – Standardized statistical weight of the mean value of infant j of group i
- $g_{ij} = f_{ij}(n_i/N_i)$

From this follows.

$$x_{ij} = \frac{1}{f_{ij}} \sum_k x_{ijk} \tag{8}$$

$$x_i = \frac{1}{n} \sum_j g_{ij} x_{ij} = \frac{1}{N_i} \sum_{j} \sum_k x_{ijk} \tag{9}$$

The determination of the mean value is not changed by using the standardized statistical weights For the variance (or standard deviation) the situation is the following: The standard deviation as given in the paragraph on "The results" page 18 was calculated for the total number of measuring values of all infants of the group using the following equation

$$\sigma^2 = \frac{1}{N-1} \sum_j f_{ij}(x_{ij} - x_i)^2 \tag{10}$$

The standard deviation which refers to the number of infants only can be calculated from the standard deviation of all measurement periods, using equation

$$\sigma_i^{*2} = \frac{n_i}{n_i - 1} \frac{N_i - 1}{N_i} \sigma^2 \tag{11}$$

For the comparison of two groups, 1 and 2, with regard to the significance of the differences

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 204 1970

ADAPTATION IN CEREBRAL PALSY OF BODY COMPOSITION, NUTRITION AND PHYSICAL WORKING CAPACITY AT SCHOOL AGE

EFFECTS OF PHYSICAL TRAINING AND IMPROVED NUTRITION

BY KRISTINA BERG

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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Adaptation in Cerebral Palsy of Body Composition, Nutrition and Physical Working Capacity at School Age

Effects of Physical Training and Improved Nutrition

BY

KRISTINA BERG

in collaboration with
JAN BJURE
BJÖRN ISAKSSON
INGEMAR OLOW
TORSTEN OLSSON

GÖTEBORG 1970

CONTENTS

GÖTEBORG
ELANDERS BOKTRYCKERI AKTIEBOLAG
1970

Introduction

Cerebral palsy is by definition an early acquired and non progressive brain damage. Its specific sign is the disturbance of motor control resulting from the brain damage. But within the limit set by this definition, a multitude of clinical manifestations are possible. Additional and severe handicaps are common and the problems are dynamic as the individual subject is affected during his developmental phase.

To study such a multi-dimensional syndrom as cerebral palsy it is helpful to consider the scope of the different problems which may be a consequence of the original brain damage.

The motor disability is a direct consequence of the brain damage. The damaging factor is considered non-specific and diffuse in its action. There may be other signs of direct brain damage however often called associated handicaps. They include such disorders as *deafness*, impaired intelligence, convulsions, behaviour disturbances, emotional instability and impaired learning abilities.

The direct sequelae of the brain damage are be complicated by a variety of indirect handicaps caused by the fact that the brain damage prevents, retards or distort the use and development of skills not primarily affected.

There is an overwhelming amount of literature on the indirect consequences within the psychological, pedagogic and social fields. The knowledge of these complications and their proper treatment are backbones in habilitation of children with cerebral palsy.

The indirect sequelae of the brain damage within the somatic field have not received a similar attention. Obvious complications such as contractures of the joints caused by the abnormal muscular tone are recognized and treated. The liability to lung infections is often mentioned. Growth retardation and inadequate supply of nutrients and energy have concerned some workers. The lack of adequate physical training has been stressed by medical scholars in this country.

In the belief that indirect and untreated somatic consequences may play a part in increasing the disability of children with cerebral palsy, a series of studies was carried out on some of the possible complications. The investigations include the physical working capacity and lung volume, aspects of nutrition such as growth, body composition, intake of energy and nutrients and the level of spontaneous physical activity. Results of therapeutic approaches are also reported. The different studies will be reported in this supplement. The first part gives the background of the subjects studied. The following six parts contain the different investigations. Finally there is a summary of the studies with respect to methods and results. A *general* discussion will then integrate some important aspects of the different studies.

Introduction

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From Bräcke Östergård Pediatric Habilitation Centre and the Department of Pediatrics Children's Hospital University of Göteborg Göteborg Sweden.

School children with cerebral palsy at Bräcke Östergård Pediatric Habilitation Centre

Cerebral palsy — definitions and incidence. Habilitation — organization and methods The subjects of the studies — their management and representativity

by INGEMAR OLOW and KRISTINA BERG

T study the different manifestations of cerebral palsy it is essential to have access to a well-defined and representative material. At Bräcke Östergård Pediatric Habilitation Centre, such material was available From there, young subjects with cerebral palsy were selected for participation in the various studies reported in this supplement (3) In this paper the general background of the subjects will be given.

Defin t on and classification f cerebral palsy Sweden

In 1959 Mc Keith and Polani (2) defined cerebral palsy persistent but not unhanging 1 order of movement and posture ppearing in the early years of life and due to a non progress e disorder of th brain, the result of interference during its development All a thorities agree on the basic principles of this definition the non-progressiveness of the disorder it earl appearance its effects on the motor pattern later in lif and that t may in lve other signs of brain lesion, such as dysartria, convulsions hearing defects and difficulties f learning In 1965 an international group of pecl list invited by the Spastic Society in England also agreed on the following definition "Cerebral palsy i a disorder of movement and posture due to a defect in the im mature brain. ( )

In 1964 Ingram published an extensive review of different classifications of cerebral palsy (7) It has been decided—until full agreement concerning the classification has been reached—that each country should define its own ter minology (2) In Sweden the classification orig inally suggested by Hagberg (1) is used.

Thus each subject is classified on the basis of three different aspects the *tonus* of the muscle the *pattern of movements* and the *anatomical distribution* of the disturbance In this way each subject gets a descriptive dia gnosis which is easily understood by anyone familiar with the principles of the classification.

Tonus For clinical use tonus can be defined as the muscular resistance to passive movements of joints In cerebral palsy the tonus of muscles is abnormal. There can be *hypertonus* which is a constant increase of tonus. This subgroup of cerebral palsy is roughly identical t th term spasticity as used in adult neur ology Another group can be dominated by a decreased tonus *hypotonus* which in isolated form is extremely rare except in infancy and early childhood. Here it may be a temporary stage—"floppy infants —prior to the dom inance of a slight ataxia or athetosis. The *tonus changing state* is a state in which the muscle tonus changes in a fairly regular way so that one group of muscles may have strong hyper tonus at a time when their antagonists have

tween the two centres and principles of treatment, evaluation, and selection for special school are similar

General outline for care—Habilitation

In discussing handicapped children, the term rehabilitation is not very accurate as it has a meaning of readaptation to work and social duties. For this reason the term "habilitation is preferred in Sweden. It means treatment of children who are born with a handicap or who get one early i.e they have no experience of normal life. H bilitation also involves other methods than rehabilitation as the aim is to help the child to as normal a development as possible in spite of the handicap This also means that the methods vary as they are adapted to the development of the hild. However the ultimate goal is the sam as in rehabilitation the best possible adaptation to a ormal adult social life, including a job

The dequate treatment of children with cerebral palsy can only be performed as a team-work involving several specialists. The many manifestation of the same basic disorder make the pooling of experience very valuable The training of different categories f assistants is also an important aspect f habilitation

Preschool ch ldre Early detection is essential, and in cooperation with local heads of the pediatric linics, babies t risk from a peri natal inj ry are regularly checked for progress. A soon a t is suspected that a child has cerebral palsy first investigation is carried out in the local pediatric linic The child is then often referred to Bräck Östergård for further i vestigation nd assessment of severity and extent of handicap. A long-term plan of habilita tion is then made for each child. It often invol ves yearly treatment period of 1—3 months at the Centre

School h ldre When school st rts at the age of seven, t i usually possible to make an accurat evaluation of the abilities and difficulties of the children with cerebral palsy based on the preschool assessment The question of where a particular child should go to school is then easy to solve in most cases. The main principle is that every handicapped child should go to the local school However there are children, for whom such integration is not considered realistic After careful investigation, a small group of severely handicapped children with normal or subnormal intelligence (approximate lower limit at IQ 70–80) are referred to Bräcke Östergård as fullboard or day-students to assure a comprehensive treatment of all their difficulties The indications for admission may be summarized as follows

1 A severe motor handicap which requires much physio-therapy occupational therapy and special—even individualized—educational equipment in school

2 A moderate motor disability but a pronounced brain dysfunction mainly associated with difficulties of learning

3 Uncertainty as to preschool evaluation f the learning facilities of a particular child who will need further observation during one or two years for a definite assessment.

4 Temporary stay at the Centre for a child with a moderate handicap who needs an intensive treatment during a short period after orthopedic or neurosurgical operations.

Incidence of cerebral palsy in western Sweden

A total of 857 children with cerebral palsy born in 1946 or later from the western region of Sweden, excluding the city of Goteborg are registered at Bräcke Östergård Of these 368 (4_.9 %) are girls. This sex difference is signif icant ($p<0.05$) from the expected 49.8 % but agrees well with the sex distribution in other cerebral palsy materials (8*)

Since 1938 when Bräcke Östergård was started, there has been a continuous recording of all children with physical handicaps in 5 of the 6 provinces, and we believe that every child with cerebral palsy[1]) is known by us.

1 Minimal cerebral palsy or hildren presenti g problems with lumsiness not included.

hypotonus. After a few seconds or minutes however, the state of the muscle tonus is reversed. Tonus-changing is usually combined with involuntary movements and primitive reflexes such as the tonic neck reflex and the Moro reflex. During sleep there is general hypotonus which is a characteristic sign of the tonus-changing state. It has different names in other countries. In English literature it belongs to the dystonic group, more specifically to the dyskinetic subgroups, as defined by Ingram (7). In America it may be called "tension athetosis" (5) or "variable rigidity".

Patterns of movement. *Athetosis* includes twisting movements of arms and legs, a grimacing play of features, often drooling and an indistinct speech. *Choreoathetosis* involves greater and more vigorous movements of the big joints of the body. These two types of movements are most common with tonus-changing. *Ataxia* is a disturbance of muscle synergy and includes tremor, often as so-called intention tremor. It is sometimes combined with hypertonus of the legs (diplegia).

Dysequilibrium is incapability of, or pronounced difficulty in maintaining posture and equilibrium (6).

Anatomical distribution. Subjects with hypertonus can have this disturbance generally distributed in all muscles of the body. When arms and hands are more affected than legs and feet it is called *tetraplegia*. *Diplegia* means a greater affliction of the lower part of the body than of the upper. *Hemiplegia* is an affliction of one side of the body. Subjects with tonus-changing have their disturbance *generally* or *half-sidedly*.

In the studies on subjects at our institute the children were classified only with respect to the tonus, as we felt that this was a major difference in cerebral palsy. The group with hypertonus, however, will be referred to as [illegible] spastics and the tonus-changing group as dyskinetics as an adaptation to English nomenclature. No children with hypotonus were studied. Further sub-grouping was not considered due to the small material. In addition to this, the *severity* of the handicap in a child was graded according to the suggestions made by Cruickshank (4). The most handicapped subjects were grade 3, [illegible] unable to care for all his bodily needs because he is unable to walk unassisted, talk clearly or has little use of his hand. The grade 1 subject [illegible] may appear normal except that the precision of his movement may be impaired. Grade 2 subjects are in between these extremes.

Present organisation

Today Sweden is divided into seven different administrative hospital regions, each with a central hospital for all medical specialities. Three regions have centres for physically handicapped children, but there are advanced plans for similar centres in the other regions. The centre in the western region is Bräcke Östergård in Göteborg, a private institute owned by the Institute of Deacons in Göteborg and supported by six provinces in western Sweden and the city of Göteborg. The centre cooperates with the heads of the different pediatric clinics in the region in detecting, investigating and treating the children and it also has a close collaboration with the Pediatric Department of the University of Göteborg, the head of which is a member of the Bräcke Östergård board.

At present Bräcke Östergård has 30 beds for preschool children and 60 for school children. The institution offers full elementary school courses for nine years and secondary non-mandatory two-year courses in the social sciences. A varying number of day students, usually around 30, are also admitted for school and other habilitative measures. Children with all types of motor handicaps are admitted, not only those with cerebral palsy.

The Broström Centre in Göteborg, a pioneer institution in the care of children with cerebral palsy, serves as a day centre for children with cerebral palsy in the city of Göteborg. It also offers the first six years of elementary school. There is an agreement between Bräcke Östergård and Broström's to the effect that Bräcke Östergård admits children from Göteborg who live close to it as day students, and also children who need full board. Bräcke Östergård also admits all Göteborg children as day-students for continued school after the six-year course. There is a close collaboration be-

tween the two centres and principles of treat ment evaluation, and selection for special school are similar

General outline for care—Habilitation

In discussing handicapped children, the term rehabilitation is not very accurate as it has meaning of readaptation to work and social duties For this reason, the term "habilitation is preferred in Sweden. It means treatment of children who are born with a handicap or who get one early i.e they have no experience of a normal life "Habilit tion also involves other methods than "rehabilitation as the aim is to help the child to as normal a development as possible in spit of the handicap This also means that the methods vary as they are adapted to the development of the child. How ever the ultimate goal is the same as in re-habilitation the best possible adaptation to a normal dult social life in luding a job

The adequat treatment of children with cerebral palsy can only be performed as a team work involving several specialists The many manifestations of the same basic disorder make the pooling of experience very valuable The training of different categories of assistants is lso an important aspect of habilitation.

Preschool h ldre Early detection is essential and in cooperation with local heads of the pediatric clinics babies t risk from a peri natal injury are regularly checked for progress. As soon as it is suspected that a child has cerebral palsy a first investigation is carried out in the local pediatri clinic The child is then often referred to Bräcke Östergård for further investigation and assessment of severity and extent of handicap A long term plan of habilita tion is then made for each child. It ften invol ves yearly treatment period of 1–3 months t the Centre

School children When school starts at the age of seven, it is usually possible to make an ccurat evaluation of the abilities and difficul ties of the children with cerebral palsy based on the preschool assessments The question of where a particular child should go to school is then easy to solve in most cases. The main principle is that every handicapped child should go to the local school. However there are children, for whom such integration i not con sidered realistic. After careful investigation a small group of severely handicapped children with normal or subnormal intelligence (approx imate lower limit at IQ 70-80) are referred to Bräck Östergård as fullboard or day-students to assure a comprehensive treatment of all their difficulties. The indications for admission may be summarized as follows

1 A severe motor handicap which requires much physio-therapy occupational therapy and special—even individualized—educational equipment in school.

2 A moderat motor disability but a pro-nounced brain dysfunction mainly associated with difficulties of learning

3 Uncertainty as to preschool evaluation of the learning facilities of a particular child who will need further observation during one or two years for a definite assessment

4 Temporary stay at the Centre for a child with a moderate handicap who needs an inten sive treatment during a short period after ortho-pedic or neurosurgical operations

Incidence f ce ebral palsy in western Swed n

A total of 857 children with cerebral palsy born i 1946 or later from the western region of Sweden, excluding the city of Göteborg are registered t Bräcke Östergård Of these 368 (4 .9 %) are girls. This sex difference is signif icant ($p<0.05$) from the expected 40.8 %, but agrees well with the sex distribution in other cerebral palsy materials (6*)

Since 1958 when Bräcke Östergård was started there has been a continuous recording of all children with physical handicaps in 5 of the 6 provinces and we believe that every child with cerebral palsy[1]) is known by us.

[1]) "Minimal cerebral palsy or hildren presenting problems with clumsiness not included.

hypotonus. After a few seconds or minutes, however, the state of the muscle tonus is reversed. Tonus-changing is usually combined with *involuntary movements and primitive reflexes* such as the tonic neck reflex and the Moro reflex. During sleep there is general hypotonus, which is a characteristic sign of the tonus-changing state. It has different *names in other countries*. *In English literature it belongs to* the dystonic group, more specifically to the dyskinetic subgroups as defined by Ingram (7). In America it may be called "tension athetosis" (5) or "variable rigidity."

Patterns of movements. Athetosis includes twisting movements of arms and legs, a grimacing play of features, often drooling and an indistinct speech. *Choreoathetosis* involves greater and more vigorous movements of the big joints of the body. These two types of movements are most common with tonus-changing. *Ataxia is a disturbance of muscle synnergy and includes* tremor, often as so-called intention tremor. It is sometimes combined with hypertonus of the legs (diplegia).

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Incidence of cerebral palsy in western Sweden

A total of 857 children with cerebral palsy born in 1946 or later from the western region of Sweden, excluding the city of Göteborg are registered at Bräcke Östergård Of these 368 (42.9 %) are girls. This sex difference is significant ($p<0.05$) from the expected 40 8 % but agrees well with the sex distribution in other cerebral palsy materials (8[*])

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hypotonus After a few seconds or minutes however the state of the muscle tonus is reversed Tonus-changing is usually combined with involuntary movements and primitive reflexes such as the tonic neck reflex and the Moro reflex During sleep there is general hypotonus which is a characteristic sign of the tonus *changing state* It has different names in other countries In English literature it belongs to the dystonic group more specifically to the dyskinetic subgroups as defined by Ingram (7) In America it may be called "tension athetosis" (5) or "variable rigidity"

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TABLE 1 *Material Some data on 41 subjects at Bräcke Östergård participating in one or more studies of somatic adaptation in cerebral palsy (5)*

Index number[1])	Sex m = male f = female	Date of birth[2])	Cerebral palsy classification: Tonus	Abnormal movements	Distribution	Severity of handicap: Grade 1–3	Principal way of ambulation	Day students
1	m	53-2	hypertonus		tetraplegia	2	wheel chair	
	m	51 1	hypertonus		tetraplegia	3	wheel chair	
4	m	48-2	hypertonus	ataxia	diplegia		self ambulant	
6	f	54-2	hypertonus		diplegia		rollator	
7	m	57 1	hypertonus		diplegia	3	wheel chair	
8	f	51	hypertonus		tetraplegia	3	wheel chair	
9	m	5 1		athetosis	general	1	self-ambulant	
10	m	56-1	tonus changing	athetosis	general	3	wheel chair	
11	m	54 2	hypertonus		diplegia	3	wheel chair	
12	f	58-2	tonus changing	athetosis	general	3	wheel chair	
13	f	57 2	hypertonus		tetraplegia	3	wheel chair	
14	m	53-1	hypertonus	ataxia	diplegia	2	wheel chair	
15	m	49	hypertonus		tetraplegia	3	wheel chair	
16	m	48-2	tonus changing	athetosis	general	3	wheel chair	
17	m	53-1	hypertonus		tetraplegia	3	wheel chair	
18	f	50-1		athetosis	general	2	self-ambulant	
19	m	55-1		athetosis	general	2	self-ambulant	
20	m	58 2	hypertonus		tetraplegia	3	wheel chair	
21	f	55 1		athetosis	general	2	self-ambulant	
22	f	60-	hypertonus		diplegia	2	self-ambulant	
23	f	61 1	hypertonus		tetraplegia	3	wheel chair	
24	m	60 1	hypertonus		diplegia	2	self-ambulant	
25	m	60-2	hypertonus		diplegia	3	wheel chair	
26	m	61 1	hypertonus		tetraplegia	3	wheel chair	
27	m	61 1		athetosis	general		self-ambulant	
28	m	61 2	tonus changing	athetosis	general	3	wheel chair	
29	m	51 1	hypertonus		diplegia	2	self-ambulant	×
30	m	55 2		athetosis	general	2	self ambulant	×
31	m	60 1		athetosis	general	2	self-ambulant	
32	f	57 2	hypertonus		tetraplegia	3	wheel chair	×
33	f	52-1	tonus changing	athetosis	general	3	wheel chair	
34	m	51 2		athetosis	general	2	self-ambulant	×
35	f	55-1	hypertonus		diplegia	2	self ambulant	×
36	m	50-2	tonus changing		general	3	wheel chair	
37	m	5.-2	hypertonus		tetraplegia	3	wheel chair	
38	m	51 2	tonus changing		general	(4)	wheel chair	
39	f	57 1	hypertonus		tetraplegia	3	wheel chair	
40	f	50 1	tonus changing	athetosis	general	2	self-ambulant	×
41	m	40 1		athetosis	general	2	self-ambulant	×
42	m	42-1		athetosis	general	2	self-ambulant	×
43	f	53-2	ataxia		general	1	self-ambulant	×

[1]) Each subject had the same index number throughout the studies. Nos. 3 and 5 will not be reported, since they did not have cerebral palsy

[2]) The first two figures in the birth code refer to the last two figures of the year of birth. The figure following the year is either 1 or 2 and refers to the first or second half of that year

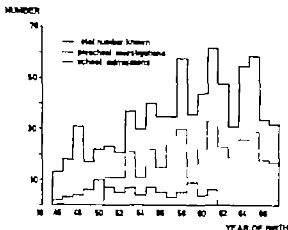


Fig 1 Incidence f cerebral palsy by year of birth in western Swed The number f children receivi g in patient treatment is indicated

During 1958–1967 454 children in the five provinces were afflicted with cerebral palsy With an approximate number of 25 800 children born during the same period in the same provinces the incidence of cerebral palsy is 1 75 pro mille This figure agrees well with the estimated figure for the whole country (8[4])

Preschool evaluations have been made on 394 children out of a total of 743 afflicted children born 1951–1967 (and thus having a chance of being investigated or treated at the institution if there was a need for it) This means that 53 / of the children with a known cerebral palsy have been in patients before school Of children eligible for school (born 1946–1961) only 17 o (95 out of 573) are or have been full board students at Bräcke Östergård

Fig 1 shows the incidence of cerebral palsy during the different years. Yearly fluctuations are obvious but due to the low number of children affected each year the fluctuations have no significance

Institutional routine for school children

At the start of school an individual habilitation program is made for each subject The program is based on the combined knowledge of the child by a team composed of physicians teachers physiotherapists occupational therapists and psychologists The different habilitative measures are given different priorities from one time to another depending on the changing need of the child Special care is taken to see that the child is not overtrained and that he has ample leisure time as other children

A common school week might include 20–30 hours of school 3 hours of physiotherapy and 3 hours of occupational therapy mostly activities of daily living Such treatment and social training are also constantly practised in the wards

The school lasts from the middle or the end of August until the beginning or the middle of June The students spend the summer vacation (?–3 months) the Christmas vacation (1 month) the winter vacation (1 week) the Easter vacation (1 week) and at least every other weekend at home

At the end of school occupational counselling is given. The students can go on to secondary schools one involving two years at Bräcke Östergård or to the centralized state school in Stockholm Most students go on to the occupational training and are then referred to the rehabilitation services for the adult

Description of the subjects and their representativity

An important aspect of habilitation is to develop specific and adequate methods of managing the subjects Bräcke Östergård therefore encourages research in this field

The studies presented in this supplement are in agreement with the aim of habilitation and are derived from our hope to give these children a better future

Table 1 lists the children with cerebral palsy at our institution who participated in the studies A complete diagnosis of these subjects and relevant personal data are given in Table 1 Table 2 gives a survey of the studies in which each subject participated

Fig 2 shows the actual number of school children at Bracke Östergård between 1960 and 1967 when the studies were initiated The student body is divided into three groups. Group 1 consists of full board children from

TABLE 1 *Material. Some data on 41 subjects at Bräcke Östergård participating in one or more studies of somatic adaptation in cerebral palsy (3).*

Index number[1])	Sex m = male f = female	Date of birth[2])	Cerebral palsy classification: Tonus	Abnormal movement	Distribution	Severity of handicap: Grade 1–3	Principal way of ambulation	Day students
1	m	54-2	hypertonus		tetraplegia		wheel chair	
2	m	51 1	hypertonus		tetraplegia	3	wheel chair	
4	m	45-2	hypertonus	ataxia	diplegia		self-ambulant	
6	f	54 2	hypertonus		diplegia	2	rollator	
7	m	47 1	hypertonus		diplegia	3	wheel chair	
8	f	51 2	hypertonus		tetraplegia	3	wheel chair	
9	m	52 1		athetosis	general	1	self-ambulant	
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23	f	61 1	hypertonus		tetraplegia	3	wheel chair	
24	m	60-1	hypertonus		diplegia		self-ambulant	
25	m	60 2	hypertonus		diplegia	3	wheel chair	
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30	m	54 2		athetosis	general	2	self-ambulant	x
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40	f	50-1	tonus changing	athetosis	general	2	self-ambulant	x
41	m	40 1		athetosis	general	2	self-ambulant	x
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1) Each subject had the same index number throughout the studies. Nos. 3 and 5 will not be reported, since they did not have cerebral palsy.

2) The first two figures in the birth code refer to the last two figures of the year of birth. The figure following the year is either 1 or 2 and refers to the first or second half of that year.

TABLE 2 *Studies of school children with cerebral palsy at Bräcke Östergård Participation of the subjects in different studies Each study is designed with the same number as the paper where it is reported*

Index No	II	III	IV	V	VI	VII
1	×	×	×	×	×	
		×		×	×	
4	×	×	×	×	×	×
6			×	×	×	
7	×	×	×	×	×	
8	×	×		×	×	
9	×			×	×	
10	×			×		
11	×	×	×	×	×	
12				×		
13			×	×		
14	×	×	×	×	×	
15	×	×		×	×	×
16	×	×	×	×	×	×
17			×	×	×	×
18	×	×	×	×	×	×
19	×	×	×	×	×	×
20	×	×	×	×	×	×
21	×	×	×	×	×	×
			×	×		
23			×	×	×	
24			×	×	×	
25		×	×	×	×	×
26			×	×	×	
27			×	×	×	×
28				×	×	
29	×					
30	×	×				
31	×	×				
32		×				
33	×	×	×	×		
34	×	×				
35	×					
36	×	×	×			
37				×		
38				×		
39				×		
40						
41	×					
42	×	×				
43	×					

the five provinces with complete registration of the afflicted children Group 2 of full board children from the sixth province (S län) and from Göteborg and group 3 of Göteborg day students As for Group 2 it is unlikely that severely or moderately affected children from the S province were not assessed at Bräcke Östergård The subjects at Bräcke Östergård are therefore considered representative of the severely handicapped children of that province The Göteborg children attend mostly as day students In Group 3 about half had such a severe handicap that they were equal to the full board students But the nearness to the Centre made day student arrangements possible (except for a few subjects included in Group 2) On the other hand, this nearness to the Centre has lead to the admission of moderately affected children who were in need of special school facilities but who would have received such facilities in the public school had they lived far away from the institution For this reason about half of Group 3 have less complicated handicaps than the rest

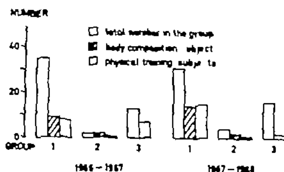


Fig Subject participating in the studies in relation to the total number of students with cerebral palsy at Bräcke Östergård at the start of the autumn term in 1966 and 1967 Group 1 includes students from the five fully registered provinces (F N O P and R), Group 2 from the S province and in patient from Göteborg, and Group 3, the Göteborg day students.

The material for the different studies was obtained from the representative student body in a selective manner The special criteria for the various studies are reported in the papers in question A general aim was to study young subjects as it was believed that therapeutic measures would be more efficient if applied to such subjects

A report of the factors which excluded children from the different studies may be of interest Subject with a complicating disease were never studied nor were

those who had been admitted on temporary basis. Body composition studies could not be carried out in subjects who were unable to drink without spilling, who had enuresis or lack of cooperation due to pronounced emotional and behaviouristic disturbances. Subject excluded from the body composition studies were generally excluded also from the physical training studies. Thus, it was preferred to use the same subjects in as many studies as possible to obtain some knowledge on the interrelationships of the observed disturbances.

In conclusion, all full board students are considered representative of the severely handicapped subjects in the region because of a good knowledge of all affected subjects in the area and a uniform evaluation and admission system. *The day-students may have a less* severe handicap but often not. The criteria for selection for the different studies was that children with a dominating physical handicap and minor associated handicaps were selected. As the aim of the studies was to reveal some mechanisms of the somatic adaptation in cerebral palsy i.e. associated with the primary brain damage and the motor disturbance, these criteria were considered appropriate.

S mmary

Bräck Östergård is the regional centre for pediatric habilitation in western Sweden. All children with cerebral palsy in the region except for the Goteborg and B provinces children, are registered at the Centre. The indications for full board admission to the Centre are guided by uniform principles with due consideration t the need of each subject.

The internationally accepted definition of cerebral palsy i used. The classification of the subgroups of cerebral palsy is Swedish and is based on the state of the muscular tone on the type of associated movements and on the anatomical distribution of the symptoms.

The incidence of cerebral palsy in western Sweden was 1 75 pro mille during 1938–1967. In patient preschool evaluations and treatments were given to 53 per cent of the affected children. Seventeen per cent were admitted as full board students to the school.

Out of this representative group of severely handicapped school children 41 subjects were selected for different investigation on the somatic adaptation in cerebral palsy.

The management and daily routine of the subjects are described.

Acknowledgement

The authors wish to express their deep and sincere gratitude to all participating subjects and to the staff of Bräcke Östergård for their kind cooperation in the present investigations.

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Methods for evaluation of the physical working capacity of school children with cerebral palsy

by KRISTINA BERG and JAN BJURE

The physical working capacity is determined by three main factors the capacity of the energy processes, the neuromuscular functions, such as strength and technique, and the psychological factors (19) In healthy adult individuals accustomed to physical work, the limits for maximal performance are set by the energy processes, more specifically by the available oxygen (4) Consequently tests of physical working capacity are arranged so as to measure the oxygen consumption (3 21) The test involves collection of expired air during work, and analysis for its gas contents which are exacting and time-consuming procedures.

In routine clinical work, indirect methods are used, which involve heart rate determinations at known work loads arranged on bicycle ergometer Assuming that there is a linear relationship between heart rate and work load the maximal work load can be predicted on the basis of two or more submaximal work loads with the maximal heart rate as an age—dependent constant (3) With a mechanical efficiency of 23 per cent in normal persons the maximal oxygen consumption can be determined (3)

Cerebral palsy can be defined as an early brain damage with permanent sequelae within the motor field (9) The resulting disability may be slight but, if not, it has a profound influence on the neuromuscular functions of the individual. Simple working capacity tests of the above type cannot be used for several reasons. Many children simply cannot use a bicycle ergometer and thus the work load cannot be determined If they can, their mechanical efficiency can be expected to deviate from the normal since they have a poor motor control and resulting poor technique and also since involuntary movements and tensions can be expected to be oxygen-consuming and lower the mechanical efficiency

Nevertheless for habilitation purposes there is a great need to determine the physical working capacity and to evaluate the effects of physical training Direct measurements of oxygen consumption during maximal physical work is then the only solution. However due to the disability children with cerebral palsy often cannot cooperate in air collections at a maximal heart rate

In this paper the results of physical working capacity tests in children and adolescents with cerebral palsy will be reported A method is presented to assess changes in oxygen uptake in persons in whom the mechanical work performed cannot be measured and who cannot participate in oxygen collections at maximal heart rates. The diagram presented also makes a rough separation between the effects on muscular improvements and the effects on oxygen uptake The maximal" physical working capacity of the subjects is also calculated.

Methods

In slightly handicapped subjects, ergometric tests were performed with the Monark bicycle ergometer (10) usually using three loads. The different steps were individualized according to the age of the subject. Straps for tying the feet

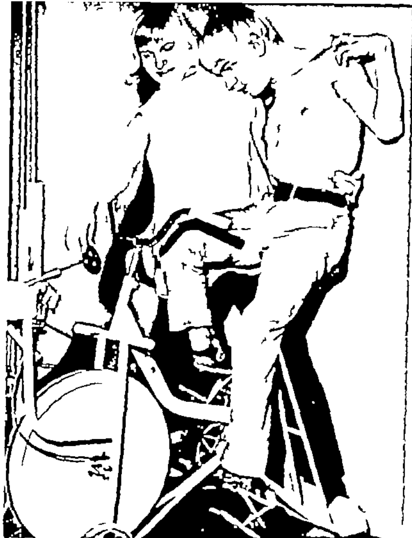


Fig 1 Training of a severely handicapped subject (No 36) on a bicycle ergometer

... the floor behind the ... meter

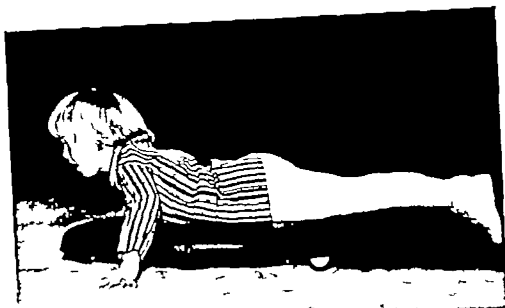


Fig 3. Training f child with spastic diplegia on saucer

t the pedals and special back supports were used when needed (Fig 1) The bicycles were regularly checked for correct loads

Severely handicapped children and adolescents performed the test lying on the floor behind the bicycle ergometer (Fig)

Young slightly handicapped children, who were too small for the Monark bicycle ergometer were tested on their own tricycle. The back wheels were elevated from the ground, and a leather strap arrangement made it possible to put resistance on the axis.

For small and severely handicapped children and for subjects with severe involvement of the legs, a "flying saucer" was used. It consisted of a padded board on four small wheels. The child moved it by pushing against the floor with its gloved hands backward or forward At full speed they worked not only with their arms but also with their head and upper part of their body (Fig 3)

A few children ith severe tetraplegia had individual programs for arm and leg movements. Movements which produced a high heart rate were selected.

The heart rate was measured by means of ECG recordings on a three-channel mingograph (Elema) or with a small telemetric outfit (Fig 4) connected to a pulse indicator (time constant 5 seconds) and to a mingograph (6) Oxygen uptake was measured with the Douglas bag technique while the expired air was analyzed according to Scholander (20) The volume of expired air was measured with a gas meter

As for the collection of expired air it was often difficult to get airtight adaptation of the rubber mouthpiece in children with severe handicaps, particularly in those with mouth involvement and in some of the younger children. Various masks were tried but the best one proved to be a rectangular rubber membrane made f extra heavy dental dam (approximate size 16–20 cm×7–9 cm with a small central hole with a diameter of 0.5 cm) The rubber mouthpiece was put on in the usual manner with the rubber plate outside the teeth and inside the lips Outside the lips the extra membrane was mounted, pulled backward and tied behind the head. A nose clip was used as usual. Air leakage was easily audible (Fig 4)



Fig. 1 Training of a severely handicapped subject (No. 36) on a bicycle ergometer

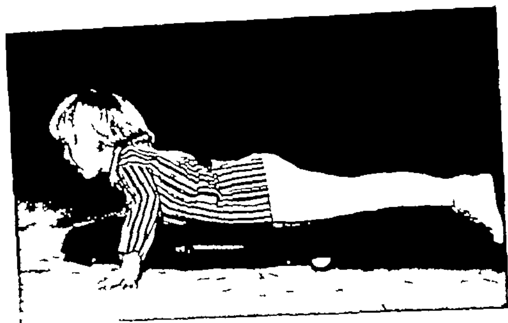


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Fig 4 Details of testing equipment The rubber membran is attached to the rubber mouthpiece and tied behind the head In addition to this nose clips and Douglas bags with wide tubes were used For heart rate recording the subject carries a small telemetric set on a cap The detector electrode is on the sternum and the indifferent one on the forehand

General procedure of testing for graphical calculation

The tests were always performed in the gymnasium at room temperature No test was performed earlier than one hour after a meal

ECG was taken immediately before work began The child was then asked to start his work slowly After a short while they usually managed very well to find an effort level which they could keep constant so that the heart rate became stabilized This was continuously checked on the pulse indicator and calculated on the basis of ECG recordings every second minute as the mean of at least 10 beats. The first level should have a mean value in the range of 130–160 beats per minute and the child was asked to change his effort level if he tended to be outside this range

The first collection of air was made after 4–6 minutes at the first level and for at least 60 seconds with ECG recordings every 30 seconds and continuous checks on the pulse indicator

Then the child was told to work "hard and the whole procedure was repeated at a higher heart rate level

All children were told to do "their very best and this work level was called maximal working capacity if the heart rate rose to that individual's maximal level (see below) If possible air was collected after at least two minutes at this level

Capillary blood for lactic acid determination was taken between 2 and 4 minutes after work (16)

Each determination of oxygen uptake was related to the mean heart rate value during air collection as recorded by ECG

The maximal heart rate during physical work was determined separately and without air collection A telemetric outfit enabled the child to move freely around Usually the subject was made to do his best in competition with other children Several attempts were made with different muscular activities and the highest value recorded was taken as the maximal heart rate The change in maximal heart rate during training was studied similarly

The mechanical efficiency at a known work load was determined as follows

$$\text{mechanical efficiency} = \frac{\text{kpm/min} \quad 100}{427 \times 4\,9(\dot{V}_{O_{work}} - \dot{V}_{O_{basal}})}$$

The basal metabolic rate was predicted (6) 427 is the factor for conversion of calories to force and 4 9 is the calculated value in calories derived from combustion of one litre of oxygen at a normal diet

The graphical calculation

It is difficult to test severely handicapped children with cerebral palsy who cannot perform standardized work and who have difficulties in cooperating in air collections while working maximally Therefore a test based on two or more oxygen determinations at submaxi

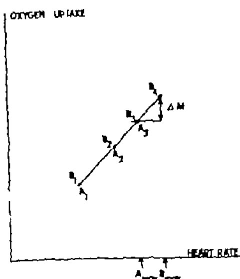
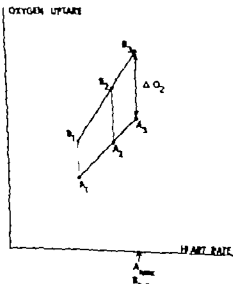


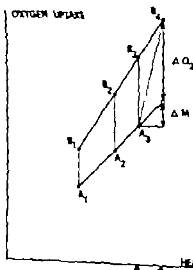
Fig. 5 The graphical calculation. "Muscle" effect.

levels with good reprod cibility of the deter mmations was used. On the basis of these deter mmations, the relationship between heart rate and oxygen consumption for this particular individual at the state of physical capacity in question was graphically described in a dia gram with the heart rate on the abscissa and the oxygen uptake on the ordinate As found by other authors, we observed that there was a rectilinear relationship between these tw parameters Consequently the "maximal" oxy gen uptake can be graphically obtained b extrapolation of the line to the individuall determined maximal heart rate

The diagram was mainly used in assessin changes induced by physical training Severel handicapped children are sedentary and hav few possibilities to do muscular work. Activa tion of such children may have two effect one gives increased oxygen uptake at a certai heart rate the other raises the maximal hea rat value The effect of training is the resu obtained, either by the combination of the two effects, or by one of them

In Figs. 5–7 the three possible effects training are graphically given. Line A–A_3 r presents an individual before training Poin A and A_2 are direct measurements of oxyge uptake at two different submaximal heart rate Point A_3 is determined by the separat ly mea ured maximal heart rate and the correspondir "maximal oxygen uptake obtained by mean of extrapolation of the line A_1–A_2. Line B_1–B represents the individual after training Poin B_1 and B_2 are direct measurements of oxyge uptake at two different submaximal heart rate Point B_3 represents a determination at the pr





vious maximal heart rate which—after training—is submaximal while point B_4 is the extrapolation to the new maximal heart rate value

In Fig 5 no change has occurred at submaximal levels after training but the maximal heart rate has increased from A_3 or B_3 to B_4 and the maximal oxygen uptake is calculated to be correspondingly higher This increase in the "maximal" oxygen uptake will be called "muscle" effect (ΔM) In Fig 6 there is an increase in the oxygen uptake at submaximal levels but no increase in the maximal heart rates The maximal" oxygen uptake is calculated by extrapolation from line B_1–B_2 and becomes higher This increase in the "maximal" oxygen uptake is called "oxygen effect (ΔO_2) In Fig 7 both effects occur simultaneously The fraction of the muscle" effect and oxygen effect of the total effect can be determined

Material

Data of the material are given in Table 1 Individual data on the subjects are published elsewhere under the same index numbers (17)

The graphical calculation of the training effect is exemplified by application to two severely handicapped subjects (Nos 20 and 33)

Results

The first step in this study was to perform ordinary bicycle ergometer tests Two determinations were made on each of the 1? subjects with a mean of 14 days between the tests. A comparison between the second and the first test is seen in Figs 8 and 9 which illustrate the change in maximal work load and the change in heart rate at identical submaximal work loads As seen some subjects show a considerable difference between the two tests although the subjects had not trained between the tests.

When making ordinary bicycle tests without air collection it is assumed that there is a mechanical efficiency of 23 per cent if the calculations are to become valid To test if this assumption was correct for children with cerebral palsy the mechanical efficiency was determined at loads of 300 kpm/min and higher in subjects who could bicycle and who were accustomed to the whole test procedure Fig 10 clearly shows that there was a great inter and intraindividual variation There was no tendency towards a better mechanical efficiency after training as seen in Fig 11

If indirect methods cannot be used direct measurement of oxygen uptake during work must be tried In this connection the reproduc

TABLE 1 *Materials*

Investigation	Total number	Age range years	Mean age years	Spast subjects number	Grade 3 handicap number
Ordinary bicycle ergometer tests, subjects Nos. 8 9 14 15 10 20 24, 25 40 41 4 and 43	1	1	17	5	3
Mechanical efficiency subjects Nos. 1 4, 7 8 10 11 14 15 16, 18 19 1 30 33 34 35, 36 and 4	18	9–25	15	8	8
Double determination of oxygen uptake subjects Nos. , 6, 8 11 14 16, 18 19 20 1 25, 30 3 33, 36 and 43	16	–18	14	8	9

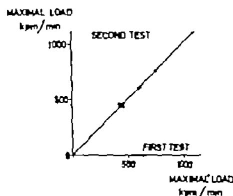


Fig. 8. Maximal work loads performed by 12 subjects during two initial tests without training in between. The line of identity is given.

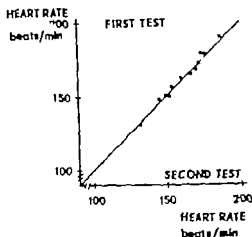


Fig. 9 Heart rates at identical submaximal loads during two initial test without training in bet een. The line of identity is given.

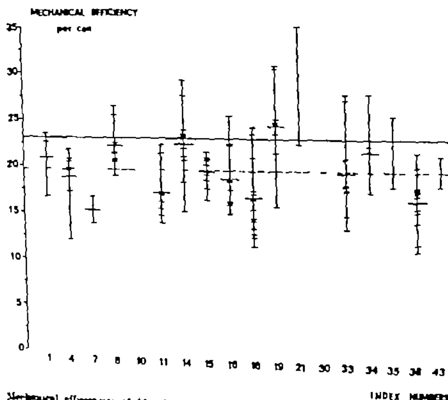


Fig. 10 Mechanical efficiencies of 16 subjects on different occasions at loads of 900 kpm/min and higher. Each observation is indicated by horizontal mark and the mean value by longer line. Mean value of all subjects is also indicated by dashed line. The normal value is 22 per cent.

vious maximal heart rate which—after training—is submaximal while point B_4 is the extrapolation to the new maximal heart rate value

In Fig 5 no change has occurred at submaximal levels after training but the maximal heart rate has increased from A_3 or B_3 to B_4 and the "maximal" oxygen uptake is calculated to be correspondingly higher This increase in the "maximal" oxygen uptake will be called "muscle" effect (ΔM) In Fig 6 there is an increase in the oxygen uptake at submaximal levels but no increase in the maximal heart rates. The maximal oxygen uptake is calculated by extrapolation from line B_1–B_2 and becomes higher This increase in the "maximal oxygen uptake is called oxygen" effect (ΔO_2) In Fig 7 both effects occur simultaneously The fraction of the "muscle effect and oxygen" effect of the total effect can be determined

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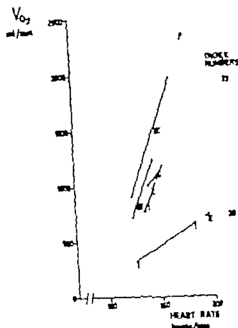


Fig. 13. Calculation of the training effect in two subjects. For interpretation, see text, Results.

sign of the neuromotor disturbances in cere[b] palsy

The rubber membrane was a valuable [aid] for air collection in children with poor m[otor] control. It was cheap, easy to mak[e] and accepted by the children. It has no dead s[pace] as do face masks. It also proved valuabl[e in] tests of small children with little or no m[otor] involvement, as it seemed to help them [re]member to keep tight around the mouth p[iece]. The membrane was not suitable in te[sting] children with excessive drooling and, in[deed] there seemed to be no way of testing t[hese] children since they tended to choke as soo[n as] the saliva outlet through the mouth was stop[ped]. No attempt was made to test children b[elow] the age of 7 years. Except for one or two chi[ldren] with excessive drooling, and two of the [most] handicapped children at the institution all [were] accessible for air collection at least at [sub]maximal loads. This means that about 9[0 per] cent of children with handicap of such a se[verity] that habilitation is needed are eligible f[or air] collection during work.

first and the second initial work test in our children indicates a difficulty in applying the conventional test to children with cerebral palsy. The subject were considered to be only slightly handicapped, and there was no doubt on the part of the examiner in considering the first test as successful and the child as fully exhausted. The improvement the second time was thought t[o] be due t[o] the fact that the child now had a personal experience of the test, and had les[s a]pprehension. Such reactions are probably pronounced in young, immature children [a]nd in children with cerebral lesions.

The great individual variations in mechanical efficiency shown [i]n Fig. 10 are probably a strong argument for using direct determination of oxygen uptak[e] during work to assess the physical [w]orking capacity in children with cerebral palsy. Training does not affect the mechanical efficiency [a]t maximal work a[s] seen in Fig. 11. A similar [v]ariation was found with respect to mechanical [e]fficiency at the same submaximal load before and after training. This variation is probably a

The methodological error of 8.1 per ce[nt in] determining the oxygen uptake of childr[en at] submaximal levels is acceptable, partic[ularly] as the biological error of determinatio[ns on] different days is included, and since the [degree] of neuromotor disturbance can vary mar[kedly] from day to day in subjects with cerebral [palsy]. Methodological errors in similar investig[ations] on homogeneous materials and uniform t[est] procedures—but on the same occasions—yielded errors of 1.7 per cent of the first determination (8). With tests on different [days] and at a maximal load the error has bee[n ...] per cent (11, 19).

The term "maximal oxygen uptake[,"] applied to healthy individuals, is used [as a] measure of the limits of circulatory and [respi]ratory adaptation to work, since it is be[lieved] that in a well-motivated person, mu[scle] strength and technique are not limiting f[actors] for maximal performance (19). However [the] maximal oxygen uptake is determined ...

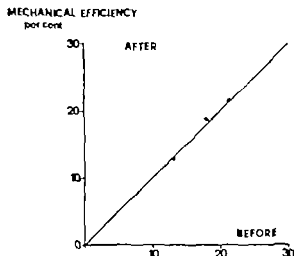


Fig 11 Mechanical fficiency at maximal load bef re and after training The l ne of i lentity is given

ibility of air collection values is of great im portance and was therefore determined in this material Any two air collections done within one week of each other at identical " heart rates were selected A small difference in mean heart rate during air collection on the two *occasions was accepted the range being 0–6* beats per minute As for oxygen uptake the mean difference between the second and the first observation was −2 ml at a mean oxygen uptake of 1077 ml The error of the method was calculated to be 8 1 per cent

Fig 12 shows that also in children with cere bral palsy there is an approximately linear relationship between oxygen uptake and heart rate

Fig 13 shows the evaluation of the training effects in two severely handicapped subjects. Subject 20 had a good muscular training effect which is indicated by an increased maximal heart rate value equivalent to an increase in the oxygen uptake from a maximal value of 650 ml to 720 ml O_2 per minute The *oxygen uptake* at submaximal levels was never above the origi nal line Thus, there was no oxygen effect of training Subject 33 could never participate in air collection at her maximal heart rate and the figure shows tests at submaximal levels The oxygen effect of training is obvious At a heart rate of 145 beats per minute the oxygen uptake was *initially 971 ml* O_2 per minute (directly measured) It then increased to 1233 ml (directly measured) after 2½ months and to 1470 ml *after* another 2¼ months (intra polated) The maxi mal heart rate recorded without air collection was initially 167 beats and later rose to 177 beats per minute The corresponding oxygen uptake had to be extra polated on the lines For maxi mal" oxygen uptake the initial figure was about 1600 ml per minute and the final figure 2300 ml

Discussion

Determination of the physical working capacity of children and adolescents usually seems to be carried out using the same methods as used in adults i e bicycle ergometer tests with heart rate determinations Thus Howell and Macnab have tested some 2200 children aged 7–17 by that method (14) The same method was used by Adams *et al* (1 2) who tested Swedish city *children and children from* a rural area and from California Ekblom *et al* (12) also used bicycle ergometer test methods on children with cerebral palsy but included direct measurement of oxygen uptake

The difference in performance between the

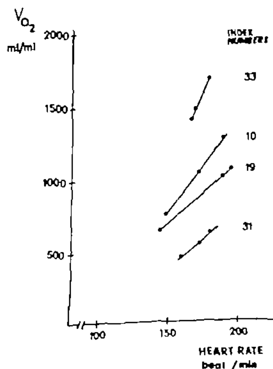


Fig 1_ Examples of the pproximately linea relation ship between xygen uptak and heart rat

working capacity is of great value for evaluation of children with cerebral palsy we considered even an approximative figure from extrapolation valuable for a realistic habilitation of the child. In consequence with this, the observed maximal oxygen uptake, restricted by non-circulatory limits has a value in the assessment.

Summary

Application to children with cerebral palsy of ordinary physical working capacity tests involving standardized work on bicycle ergometers is not possible since the handicap of such children involves poor neuromotor control. The work load performed will vary since the involuntary movements and tensions also are oxygen-consuming and varying. The mechanical efficiency also changes considerably in such subjects, even at the same load in the same individual on different occasions.

Thus, direct measurements of oxygen consumption during work is the only solution. However due to mouth involvement it is often difficult to perform air collection, in subjects with cerebral palsy particularly at maximal work intensity.

A simple rubber membrane was therefore made which facilitated air collection in children with cerebral palsy.

A graphical method which correlated oxygen uptake to heart rate at two or more submaximal levels was also developed. For a rough estimate of the maximal oxygen uptake in subjects where direct determinations were not possible, extrapolation of the line to the maximal heart rate individually determined, was done.

Training of these inactive subjects could change the original line in two ways. An improved muscular performance with respect to strength and technique the "muscle effect" seemed to increase the maximal heart rate and extended the line: a higher oxygen capacity the oxygen effect raised the original line i.e. an increased oxygen uptake at a given heart rate was demonstrated. Either effect alone or the effect in combination increased the maximal oxygen uptake. It was recognized that non circulatory limits restricted oxygen uptake in many subjects. The term *observed maximal" oxygen uptake* was used in this context.

Acknowledgement

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cular function the possibility of muscular limitation must also be kept in mind. For the individual however the consequence nevertheless is a limited physical performance and the subject cannot actually make use of a good capacity of circulatory and respiratory adaptation to work if he has it Unfortunately no term has as yet been coined for maximal performance restricted by non-circulatory limitations. In this paper the term observed maximal oxygen uptake will be used in this context Training will affect these subjects in a manner which differs from that in healthy persons Improved muscular strength and technique are probably early effects of training and cause an increase *in the maximal heart rate* This increase simply means that there is an improved ability to use circulatory and respiratory capacities *which have been out of reach for the subjects* because of inefficient muscular strength On the other hand an increased oxygen uptake per heart beat indicates a better circulatory and respiratory adataption and is probably what most closely resembles the training effects found in healthy subjects The diagrammatic calculation makes it possible to visualize these training effects which we call oxygen" and "muscular effects

Recent studies of muscles at work have indicated that muscle glucogen is an important limiting factor for contractions This energy giving substrate has also been found to increase locally in physically trained muscles (7) Such an effect could be one cause of the better muscular efficiency after training noted here

Determinations of lactic acid after work generally yielded low values before training even *in subjects who were so exhausted that* they could not walk after the test (5) This confirms the assumption that the central circulatory capacity was not fully exhausted but that the maximal performance limits had other origins After training very high lactic acid values could be found

The increase in the observed maximal heart rate which was caused by physical training and which we ascribed to the muscle improvement does not seem to have been reported before Instead a decrease in the maximal heart rate in ordinary people and in athletes has been reported after training (13 15) However there is an obvious difference between the muscular state of such subjects and that of our subjects.

The advantage of using the diagram to calculate the physical working capacity is that it offers a test method for subjects who cannot perform standardized work and who cannot participate in air collection at the maximal heart rate The principle is based on the same assumption as the conventional physical working capacity tests Direct experiments which verify the concept of a linear relationship between oxygen uptake and heart rate even in children with cerebral palsy have been performed Extrapolation to a point outside the direct determinations can be *inaccurate however* In untrained children it is hard to know if the straight relationship between oxygen uptake and heart rate continues *to maximal heart rate* For several of the children actual determinations have proved this to be true In a few severely handicapped subjects however the uptake at the observed maximal heart rate was sometimes lower than the uptake some 10 beats below the maximal heart rate One explanation is that there were difficulties in obtaining good air collections at those levels or perhaps the effort was actually supramaximal since very high lactic acid concentrations were found in some of these cases When such effects were observed, the actually observed maximal oxygen uptake was considered the maximal capacity For the others extrapolation to the observed maximal heart rate was used in spite of the suspicion *that the* relationship may not be linear near the maximal heart rate in all subjects (18 22) The error induced by extrapolation in such subjects is an underestimation of the maximal oxygen uptake This risk was taken rather than making theoretical corrections as it was realized that the figure obtained was an approximation The concept of maximal *oxygen uptake* being the best measure of maximal working capacity is widely recognized and since maximal physical

with various loads based on his maximal capacity as follows. 3 min. at about 50% of his maximal load 3 min. at 75%, 3 min. at 25 %, 6 min. at 75 %, 3 min at 50% and 1–3 min. at 100%. Children who could not bicycle had similar programs of quicker and slower motions. The therapist controlled the heart rate and the respiratory rate on each training occasion and increased the loads if the heart rate did not reach the maximal level during the training sessions. The total training periods varied between $1\frac{1}{2}$ and 16 months.

Determination of *total hemoglobin* was performed with the alveolar CO method of Sjöstrand (15 17).

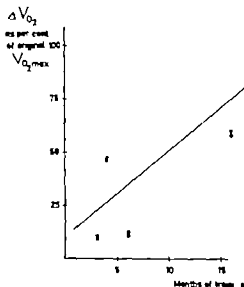


Fig. 2. Relationship between effect of physical training and duration of training. The regression line is drawn and the correlation coefficient is 0.65.

Results

Individual physical training results are given in Table 2. The effect in each child was evaluated according to principles discussed in previous article (1). Thus, the oxygen effect of training is the change in oxygen uptake at the same heart rate in any individual. The figures usually represent direct determinations at heart rates close to the observed maximal heart rate if the subject could not cooperate at the maximal heart rate. The muscle effect is the difference between the observed maximal heart rate before and after training. The change in oxygen uptake due to the increase in the observed maximal heart rate is not given, as it would be an estimated figure of interest only in determining the part played by muscular training for the total effect. The total effect is the change in the maximal oxygen uptake after training and is caused by the oxygen and muscle effects, singly or in combination with each other as seen in the table. Of the 20 subjects with a good effect, the result was due to a muscular effect alone in 3 subjects, to the oxygen effect alone in 13 subjects, and to a combination of effects in the remaining 4 subjects.

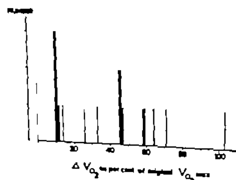


Fig. 1. Effect of physical training on the observed maximal oxygen uptake as per cent of the original value.

The effect of training on oxygen uptake was great in many subjects. A frequency distribution diagram is seen in Fig. 1. Only two subjects had no training effect. Eight subjects improved by 10–15 per cent and the remaining 12 subjects by more than 25 per cent. As a training effect, the observed maximal heart rate value increased significantly ($p < 0.01$) with a mean value before training of 181 ± 2.6 (S.E.) and after training 190 ± 2.8 (S.E.).

The relative improvement in the observed maximal oxygen uptake increased with longer periods of efficient training (Fig. 2).

TABLE 2 *Effects of physical training of school children with cerebral palsy. The observed "maximal" oxygen uptake, the oxygen uptake at an individually fixed heart rate and the observed maximal heart rate before and after training are given. From these values the total effect as per cent of the original "maximal" oxygen uptake and the fractions of "oxygen" and "muscle" effects for the total effect were calculated*

Index No	Total effect: Observed "maximal" oxygen uptake l/min		"Oxygen" effect: Oxygen uptake at an individually fixed heart rate l/min		Muscle effect: Maximal heart rate beats/min		Improvements of originally observed values		
	Before	After	Before	After	Before	After	Total effect %	Oxygen effect fraction	Muscle effect fraction
1	0 9[illegible]	1 4	1 13)	1 4	187	[illegible]05	46	0.7	0.3
	1 [illegible]7	1 45	–	–	176	193	14	0	1 0
4	[illegible].02	[illegible].88	[illegible]6	[illegible]88	[illegible]00	190	10	1 0	0
7	0 85	1.39	0 89	1.39	176	[illegible]00	64	0 9	0 1
8	1 [illegible]	1 94	1 40	1 94	180	[illegible]00	53	0	0.3
11	0 96	1.5	0 90	1 5	19[illegible]	196	50	1 0	0
14	1 61	1 77	1 61	1 77	19	188	10	1 0	0
15	1 [illegible]3	[illegible]5	1 [illegible]3	[illegible]5	176	19	103	1 0[a])	0
16	1 60	[illegible].83	1 60	[illegible].83	17	194	71	1 0[a])	0
18	1 70	1 87	1 70	1 87	180	188	10	1 0	0
19	1 [illegible])	1 37	1 [illegible])	1.39	193	195	1	1 0	0
[illegible]0	0 66	0 73	–	–	183	193	11	1 0	0
1	0 70	1 00	0 79	1 00	187	189	[illegible]0	0	1 0
3	0 43)	0 48	–	–	190	[illegible]04	11	0	1 0
30	0 76	0 75	–	–	188	(175)	0	0	0
31	0 73	1 18	0.80[1])	0 [illegible]3	188	183	45	1 0	0
32	0 40[1])	0 40	–	–	140	140	0	0	0
33	1 6[illegible])	[illegible].35)	0 97	1 47	167	177	45	0.5	0.5
34	1 63	[illegible].40	1 63	[illegible].40	19	188	47	1 0	0
35	1 [illegible]3	1 79	1 [illegible]3	1 [illegible]9	175	179	46	1 0	[illegible]
36	[illegible]15	[illegible]30	–	–	170	195	11	0	1 0
43	1 71	[illegible]7	1 71	[illegible]7	180	185	33	1 0	0

) = extra- or intrapolated figure

[a]) = at maximal heart rates after training the oxygen uptake was lower than at heart rates some 10 beats below the maximal heart rate

50–60 subjects with cerebral palsy at the institution. However, the facilities for air collection and gas analysis were limited, which influenced the course of the study. Consequently, as some subjects studied during the first six months had good training results and presented no problems in training and testing once the initial difficulties were overcome, they were excluded from further studies so that more severely handicapped children could be included.

Determinations of *blood volume and total hemoglobin* were performed on subjects Nos. 2, 11, 18, 20 and 33.

Methods

Body heights and *weights* were determined as presented elsewhere (2).

The testing procedure and the method for evaluation of the training effects have also been published elsewhere (1). For activation of children during *training* the same methods were used as reported in that article. The children were free to move around, even outside, during training sessions, however.

Each child had three individual training periods a week and was supervised by his physiotherapist. Each period lasted for 20 minutes

TABLE 5 *School children with cerebral palsy Effect of physical training on total hemoglobin and total blood volume in five subjects*

	Before training			After training		
Index No.	$\dot{V}_{O_2 max}$ l/min	THb g	TBV l	$\dot{V}_{O_2 max}$ l/min	THb g	TBV l
2	1 27	[illegible]	2.88	1 49¹)	765	5 07
11	0.96	410	2.83	1.35	5[illegible]	4.02
18	1 70	[illegible]	4.30	1 87	457	4 44
20	0.[illegible]	[illegible]	2 49	0 71¹)	[illegible]	2.[illegible]
23	0 97	[illegible]	3 62	1 23	727	5 41

¹) Muscle effect.

are striking particularly as the training program must be considered moderate if not slight. However as has been pointed out previously (5 10), subjects with an abnormally low oxygen uptake due to inactivity may be expected to improve their capacity more than active healthy persons Physical training of children with cerebral palsy has been reported as successful by other authors (13) However poor physical training effects have been found in severely handicapped children with cerebral palsy (7)

The favourable training effects measured in the laboratory reflected an improved physical wellbeing in many subjects For instance subject No 18 reported spontaneously that he could accompany his brother on walks without feeling at all tired twice the distance he had been able to move around before the training Subject No 23 could crawl 3 times the original distance on the floor after 5 months of training Subject No 20 started to enjoy various hobby activities and joined the boy-scouts.

The reasons why there were small training effects in ten subjects are diverse The two children with no change were below the age of 12 years and were hard to motivate to efficient training Subjects Nos and 20 showed some improvement but lost interest after a few months Subject No 4 had training for one term before testing and his improvement was probably more 10 per cent Subjects Nos 14 18 19 and 26 initially had fairly good oxygen uptakes and the training program was probably not enough for them. Subject No 25 was in the institution only for a very short time

No tendency was found in the material of a better result being correlated either to age to severity of handicap or both Probably the motivation of the subject is the most important factor for a good result.

Measurable improvement was sometimes not noticed at the beginning of the training, but appeared after some time When improvement was noted, it seemed to continue at about the same rate for many months (Fig ?) Probably some children reported here will continue to increase their oxygen uptake after continued training The observation of an initial period with no obvious effect might explain why Ekblom *et al* (7) found no training effect in severely handicapped children, as their study lasted for only 6 weeks The duration of our study probably also explains the great increase in observed maximal oxygen uptake. Undoubtedly equally good results could have been obtained with more training periods during a shorter time However the training had to be added to an already strenuous habilitation program and more time could not be allowed As lack of time would probably be the case in any attempt of physical training of handicapped adolescents with school education, our training program was considered realistic during these circumstances.

Summer vacation can be expected to induce a lower physical working capacity in subjects with cerebral palsy since few homes have the *facilities* or *the* know-how required for physical training This was also statistically confirmed.

The *increase* in total hemoglobin induced by physical training parallel to the increase in observed "maximal" oxygen uptake is in full agreement with previous experiences (9) It supports our way of calculating the maximal oxygen uptake *in this* material. Of particular interest is the result obtained in subject N as the increase in the observed maximal oxygen uptake in this subject was dependent on the increase in the observed maximal heart rate alone.

TABLE 3 *Course of physical training of school children with cerebral palsy Duration of various periods in months*

Index No	Training without effect	Training with increasing oxygen uptake	Further training without effect	Total training period
1	—	7	—	
	—	3	5	8
4	—	3	5	8
7	9	7	—	16
8	—	0	—	9
11	9	7	—	16
14	—	4	1	16
15	—	11	5	16
16	—	11	5	16
18		1	5	8
19	—	6	-	8
20	—	8	—	8
1	—	$1\frac{1}{2}$	$0\frac{1}{2}$	8
3)	—	1	—	$1\frac{1}{2}$
30	3	—	—	3
31		6	—	8
3)	4	—	—	4
33	—	6	3	8
34		4	—	4
35	—	4	—	4
36		4		8
43	—	4	—	4

) Subject left the institution

) Subject interrupted his training

Table 3 gives the duration of the training for each subject and also shows that observable training effects sometimes do not come immediately Subjects who were dropped from the study because of their refusal to continue training are also indicated

The effect on observed maximal oxygen uptake after 3 months of summer vacation, without *organized training* is seen in Table 4 Seven of eight subjects show a reduction during vacation compared with the training period Students *t* test showed that the difference was significant ($p<0.01$)

The effect of 3–5 months of training on the lactate level of 10 subjects (Nos. 8 9 14 15 16 20 34 40 42 and 43) is illustrated in Fig

TABLE 4 *Physical training of school children with cerebral palsy Observed "maximal" oxygen uptake after summer vacation in comparison with a preceding period of training*

Index No.	Before training l/min	After 3 months of training l/min	After $3\frac{1}{2}$ months of vacation l/min
	0 91	0.90	0.8
8	1	1 8	1 46
11	1 16	1 06	0.96
14	1 61	1 [illegible]	1.55
15	1 23	1 87	1 63
16	1 66	[illegible]13	[illegible]13
34	1 63	[illegible]40	—
35	1 23	1 [illegible]9	1.3

3 The value before training is the highest one found after two initial tests

The effect of physical training on total hemoglobin and total blood volume is seen in Table 5 It is evident that an increase in observed maximal oxygen uptake is accompanied by an increase in total hemoglobin and blood volume at roughly the same proportion

Discussion

Physical training of healthy adults usually *results in increases of about 5–20 per cent* of the maximal oxygen uptake (6 11 12) Considering this the results obtained in this group

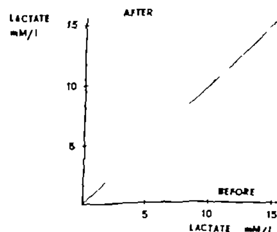


Fig 2. Lactate levels 4 minutes after work before physical training and after 3–5 months of training The line of identity is given

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Negative side effects of training can be expected particularly in spastic subjects as increased muscular strength might increase the spasticity No such effect was noted in the present study Subject No 35 reported an uncomfortable feeling of her legs being locked during training after 4 months and stopped training without further side effects Children with dystonia and/or athetosis experienced the relaxation period after training as very pleasant and reported better volontary control (3)

The ease of obtaining good results of a simple training program and the great interest displayed by most subjects who often explicitly asked for more training after the study was stopped indicate how neglected physical activation has been in habilitation programs for children with cerebral palsy

Summary

The results of training school children with cerebral palsy are reported. Twenty two severely handicapped subjects, with a mean age of 14 years were trained three times a week for 20 minutes each time and for varying periods, ranging between 1½ and 16 months. The effect of training on the observed maximal oxygen uptake was pronounced 8 subjects improved 10–15 per cent above the original value and 12 subjects 25 per cent and more Several student subjectively noted improved performance and well being

It was noted that inactivity during the 3½ months of summer vacation significantly reduced the observed "maximal oxygen uptake incurred after a previous training period of equally long time

A measurable training effect was sometimes not found immediately Once an effect was noted it seemed to continue at the same rate for several months

It can be concluded that simple training as described here probably can be fitted into any rehabilitation program and that it is important in increasing the physical capacity of severely handicapped children with cerebral palsy

Acknowledgement

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Dynamic and static lung volumes of school children with cerebral palsy

by JAN BJURE and KRISTINA BERG

As far as we know no reports have been published on dynamic and static lung volumes in subjects with cerebral palsy. This is remarkable since cerebral palsy involves a poor neuromotor control and can influence the coordination and efficiency of the muscles used for breathing. Moreover children with cerebral palsy have a low maximal oxygen uptake (1, 5, 9). The reason for this is not clearly understood. It can partly be explained by a lack of training, but in several subjects a reduced physical fitness is still present after months of training. Other explanations for the reduction in the oxygen uptake must also be considered. In view of the deficient neuromotor control in these subjects, a possible limiting factor may be their ventilatory capacity. For this reason we decided to measure static and dynamic lung volumes in subjects with cerebral palsy.

Material

We have studied 22 subjects with cerebral palsy, all included in the material described earlier (10). Fourteen had the spastic and eight the dyskinetic type of the disease. Some anthropologic data are given in Table 1. Although the subjects with dyskinesia had higher age and anthropologic values, the differences were not statistically significant. No subject had any history of lung disease and/or signs of respiratory infection at the time of the study.

Methods and procedure

The lung volumes were measured with a modified Bernstein spirometer. Normal values were predicted according to Bjure (3) for children and Berglund *et al.* (2) for adults. Static lung volumes were measured with the Helium dilution method (8). Normal values were predicted on the basis of equations given by Helliesen *et al.* (7) for children and by Grimby and Söderholm (6) for adults. The expiratory peak flow rate was measured with Wright's peak flow meter. The normal values were predicted according to Bjure and Carlström (4). Static and dynamic lung volumes were corrected for BTPS.

The subjects were placed in front of the spirometer and were thoroughly instructed on how to perform the tests. They were allowed to get used to the apparatus by quietly breathing through the mask and mouth piece, the positions of which were regularly checked to avoid leakage. The technical assistant was the same throughout the whole study and was well acquainted with the subjects for almost two years. The assistant had participated in the studies on the physical capacity and oxygen uptake of the subjects as well as in a telemetric study of daily energy expenditure.

TABLE 1. *The material. Anthropologic data. Means, standard errors of the mean and ranges*

	Age years	Height cm	Weight kg
Dyskinetic subjects	12.8±1.8 7–20	146.9±7.0 118–172	38.1± 6.6 19.6–56.0
Spastic subjects	11.7±1.1 7–23	135.5±4.1 114–166	28.8± 4.2 22.0–67.6

TABLE 3 *Lung volumes in dyskinetic subjects For explanation of abbreviations see Table 2*

Subject No.	VC	VC %pred.	FEV	FEV %pred.	FEV%	FEV% %pred	RV	RV %pred.	FRC	FRC %pred.	TLC	TLC %pred	P.F.R.	P.F.R. %pred.
16	1.78	38	1.75	45	100	116	2.25	196	2.96	117	4.42	90	355	83
18	1.52	46	1.43	51	94	106	1.24	141	1.62	96	2.96	60	270	78
19	2.10	78	1.73	60	79	93	1.21	181	1.72	104	3.14	97	250	80
21	1.43	62	1.43	71	100	112							105	39
27	0.70	34	0.66	37	94	111	0.61	95	0.95	90	1.31	86	86	33
31	0.67	55	0.63	44	71	84	0.64	110	0.96	90	1.81	79	95	43
33	0.90	22	0.82	14	88	85							180	35
34	3.26	65	1.90	46	59	69	2.06	229	3.21	114	5.84	102	420	93
Mean		49.9		47.1	81.9	94.8		165.8		101.5		83.7		60.6
Standard error of the mean		±6.3		±6.4	±6.2	±7.2		±20.4		±4.5		±6.8		±8.9
t-values for the difference between obs.-pred	−4.94		−4.77		−0.78		2.34		0.85		−2.06		−4.31	
t-values for the difference between spastic and dyskinetic subjects		2.20		2.96		1.88		−3.10		−2.47		0.12		2.39

TABLE 2 *Lung volumes in spastic subjects*

Subject N	VC	VC %pred.	FEV	FEV %pred	FEV%	FEV% %pred	RV	RV %pred.	FRC	FRC %pred	TLC	TLC %pred	P F R	P F R. %pred
1	2.34	68	2.28	77	97	114	0 60	78	1 11	53	2 72	72	370	106
4	4 49	98	4.04	103	90	101	1 34	113	2.53	100	5 60	113	515	1 1
6	1 23	52	1 23	60	100	112	0 44	63	0 79	53	1 58	58	100	37
7	1 65	79	1 65	94	100	118	0 78	1 4	1 01	86	..55	109	.30	91
11	33	60	2.15	65	9	108							405	107
13	1 47	7					0.34	55	0 65	57	1 8	80	5	93
14	3 18	100	3 06	112	96	112	0.53	63	1 57	88	3.73	106	380	115
17	1 32	45	1 17	47	88	104	0 47	59	0 65	39	1 85	57	200	64
20	1 72	78	1 60	53	93	85	1 19	178	1 36	106	1 96	77	175	66
22	1 16	57	1 16	66	100	99	0 70	129	0 79	60	2.0	80	185	77
23	0 72	37	0 7	44	100	112	0 65	110	0 99	93	1 36	64	180	8
24	1 32	60	1 28	66	97	114	0.42	63	0 0	72	..40	94	250	94
25	1 18	79	1 09	83	93	109	0 46	88	0 66	73	1 72	95	170	78
26	0 85	61	0.70	56	83	98	0 44	88	0 84	75	1.52	88	160	71
Mean		67 4		73.5	94.5	108 5		93 2		74 9		84 8		85 6
Standard erro of the mean		±4.8		±5.8	±1.5	±1 7		±10 0		±5.3		±5.2		±6 1
t-values for the difference between obs. pred.	−5 84		−4.01		6 09		−0 80		−3 02		−.33		−1 80	

VC — vital capacity FEV — forced expired v lume in one second, RV — residual volume FRC — functional resid ual capacity TLC — total lung capacity (l BTPS), FEV% — FEV_1/VC, and PFR — peak flow rate (l/min ATPS).

TABLE 3 *Lung volume in dyskinetic subject For explanation of abbreviations see Table 2*

Subject No.	VC	VC %pred.	FEV	FEV %pred	FEV%	FEV% %pred.	RV	RV %pred.	FRO	FRO %pred.	TLO	TLO %pred	P.F.R.	P.F.R. %pred.
16	1.75	38	1.78	48	100	118	2.36	198	2.06	117	4.42	89	255	82
18	1.83	48	1.43	61	94	106	1.24	141	1.83	96	2.98	80	270	78
19	2.19	75	1.73	60	79	93	1.21	181	1.73	104	3.14	97	250	90
21	1.43	62	1.43	71	100	112							105	39
27	0.70	34	0.66	37	94	111	0.61	96	0.95	90	1.31	88	86	33
31	0.87	56	0.63	44	71	84	0.64	119	0.95	98	1.51	79	95	43
33	0.90	22	0.52	14	58	65							160	35
36	2.36	66	1.99	46	80	69	2.66	229	2.21	114	5.84	102	430	93
Mean		49.8		47.1	81.9	94.8		165.5		101.8		82.7		60.5
Standard error of the mean		±6.3		±6.4	±6.2	±7.2		±20.4		±5.8		±6.8		±8.9
t-values for the difference between obs. pred	−4.94		−4.77		−0.75		2.24		0.86		−2.66		−4.31	
t-values for the difference between spastic and dyskinetic subjects		2.20		2.96		1.65		−3.10		−2.47		0.12		2.39

Results

The results are presented in Tables 2 and 3 There were no signs of airway obstruction in either group (Fig 1) judged by the normal forced expired volume in one second as per cent of vital capacity (FEV) There was no significant difference in the reduction of the total lung capacity (TLC) between the two groups The vital capacity (VC) was significantly reduced ($p<0.01$) The lowest values were found in subjects with dyskinesia and were 50 per cent of the predicted normal values compared with 67 per cent in the subjects with spasticity The difference was statistically significant ($p<0.05$) Peak flow values were reduced in subjects with dyskinesia and averaged 61 per cent of the predicted normal values ($p<0.05$) with significant difference between the two groups ($p<0.05$)

The static lung volumes functional residual capacity (FRC) and residual volume (RV) were distributed in a different way for the two groups (Fig 2) For the subjects with spasticity RV was normal but FRC was significantly reduced ($p<0.01$) averaging 75 per cent of the predicted value i e reduced roughly to the same extent as TLC In subjects with dyskinesia RV was markedly increased to 156 per cent ($p<0.05$) with an almost normal FRC The difference in RV and FRC between the groups was statistically significant ($p<0.01$)

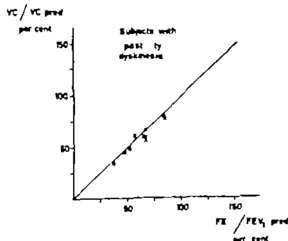


Fig 1 The relation between vital capacity (VC) and forced expired volume in one second (FEV) given as per cent of predicted normal values in subject with spasticity and dyskinesia. The line of identity is given

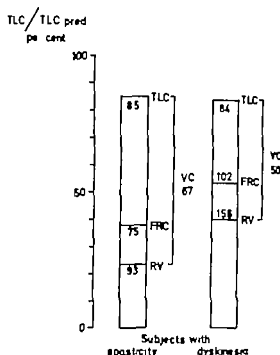


Fig — Lung volumes in subjects with spasticity and dyskinesia given per cent of the predicted total lung capacity (TLC) The numbers refer to the percentage deviation from the predicted normal values for residual volume (RV), functional residual capacity (FRC), vital capacity (VC) and total lung capacity (TLC) Increased values are above the demarcation line in question, and decreased values below

Discussion

When dealing with young subjects, whether they are handicapped or not the question arises whether the cooperation is such that the spirometric values reflect the actual pulmonary state of the subject It must be assumed that the cooperation of the children with cerebral palsy in this material was optimal on the following grounds

1 Seventeen of the 22 subjects had taken part in previous studies with mouth piece breathing and were familiar with such procedures

2 The technical assistant was very well acquainted with the subjects and knew how to persuade them to do their very best

3 The severity of the handicaps was approximately the same for the two groups and there was no reason to believe that the motivation of the subjects in one group should be less than that in the other group The subjects with dyskinesia in whom a lack of motivation could be

suspected, had a mean age which was 2 1 years higher than that of the other group. Thus, poor motivation due to a lower age cannot explain differences in values between the groups. Furthermore our clinical experience indicates that the subjects with dyskinesia in this material were more alert and cooperative than those with spasticity

Subjects with the spastic type of cerebral palsy have a reduced total lung capacity with an almost normal distribution of vital capacity residual volume and functional residual capacity In this respect they have a restrictive lung impairment. Although their vital capacity is reduced to 67 per cent the value is not so low that the ability to ventilate is reduced, since the full vital capacity is rarely used even at maximal exercise.

Subjects with the dyskinetic type of the disease also have a reduced total lung capacity Since the residual volume is markedly increased, the vital capacity is reduced to less than half of it predicted value This means that these subjects are hyperinflated at maximal expiration They are not hyperinflated during normal breathing however judged by the normal functional residual capacity In some respects, they behave like patients with obstructive lung disease but since they have no signs of obstruction, the increased residual volume must be the result of the neuromotor disturbance per se The subjects cannot voluntarily force their thorax back t normal size presumably because of a disturbed function of their respiratory muscles.

Summary

The dynamic and static lung volumes were measured in 22 subjects with cerebral palsy There ere no signs of airway obstruction. The total lung capacity was significantly reduced averaging 85 per cent of the predicted normal values In the 14 subjects with spasticity the functional residual capacity was significantly reduced to 75 per cent of the predicted value wherea the eight subjects with dyskinesia showed a marked and significant increase in the residual volume (158 per cent of the predicted value) This difference in the distribution of the lung volumes resulted in a 50 per cent decrease in the vital capacity for subjects with dyskinesia compared with a 67 per cent decrease for subjects with spasticity These deviations in lung volumes from the predicted normal values and the differences between the two groups can be explained by the reduced ability of voluntary muscular control.

Acknowledgement

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From Bräcke Östergård Pediatric Habilitation Centre, and the Department of Pediatrics Children's Hospital and the Metabolic Laboratory Sahlgren's Hospital University of Göteborg Göteborg Sweden.

Body composition and nutrition of school children with cerebral palsy

by KRISTINA BERG and BJÖRN ISAKSSON

Spastic school children often give the impression of being chubby or fat. This has also been reported in the literature (4 5 10 19 22) However food consumption records usually show a lower energy intake than recommended for healthy children (4 5 10 13) The apparent overweight in connection with a presumably low energy intake of the spastic children in our institution made us consider their nutritional state. In addition to dietary records, we measured their body composition with isotope dilution methods. Our preliminary results initiated studies also on dyskinetic and spastic children with a normal or low body weight. The level of their spontaneous physical activity was also studied and will be given in a separate article (3) Longitudinal studies of the effect of physical activation and of an improved nutrition were then undertaken. The results of these studies will be reported subsequently (2)

Material

The study was made at Bräcke Östergård Pediatric Habilitation Centre Only full board subjects with cerebral palsy were included. Nineteen of the 35 full board school children at the institution in 1966 and 1967 fulfilled the following criteria necessary for the study No complicating disease ability to drink without spilling complete bladder control and cooperability The body composition measurements failed for technical reasons on 3 subjects (Nos. 10, 1 and 13). In September 1966 11 new subjects with cerebral palsy started at the institution as full-board students. Of these 7 qualified for the study (Nos. 22 28) Thus, the material consisted of 23 subjects. Table 1 gives the distributions of sex, type of cerebral palsy and severity of handicap. More information on the subjects is given elsewhere (18) under the same index numbers as used here. In the dietary studies performed between November 1966 and February 1967 only 12 of the first 16 subjects participated. In addition, 7 other subjects were studied (Subjects Nos. 10 12, 13 K.L.[1] P.A L.J J.B.[1]). The last 4 of them were severely handicapped but full-board students for many years For reasons given below only the energy intake of subjects Nos 18–21 measured in November 1967 and Nos 22–28 measured in November 1968 will be reported here

Methods

Body composition data were calculated from measurements of body *weight total exchangeable potassium* and *total body water* Calculations of the *predicted data* were based on the actual height of the subject. Intake of energy and nutrients was calculated from *individual dietary records*

TABLE 1 *The material Sex, type of cerebral palsy and severity of handicap*

	Number	Sex		Severity grade		
		male	female	1	2	3
Spastics	16	12	4	0	6	10
Dyskinetics	7	5	2	1	4	2
Total	23	17	6	1	10	12

[1] In other parts in this series, these subjects were indexed as Nos. 37 29 33, and 38.

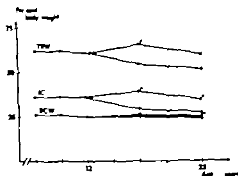


Fig 1 Diagram for prediction of normal values of body water compartments, based on data given by Friis-Hansen (8).

activity in the urine if the administered dose of labelled potassium is known and due account is taken t the activity lost during the equilibra tion time (sample U1 Table 2)

THO equilibrates with the body water within one hour One exception is the bladder urine as the bladder wall seems to allow but a slow water exchange Blood samples are usually pre ferred to determine the specific activity How ever if the bladder is emptied 5 hours after the THO administration, the subsequent void ings may very well be used for the same pur pose This was preferred in the present study as vein puncture of CP-children is difficult.

Most of the body pot ssium (more than 98%) is located intracellularly and considered to be in a constant relation with the nitrogen. Th water content of the body cells is also considered to be constant. It is thus possible to calculate body composition data from deter minations of BW K and TBW (16)

Body cell mass (*BCM*) in kg is calculated ecording to Moore (16) from the total ex hangeable pot ssium (K in mmol)

$$BCM = \frac{K \quad 8.33}{1000}$$

The equation is based on the assumption of a potassium-nitrogen ratio of 3 mmol/g and a protein content of 25 of the wet weight of the cells.

Intracellular water (*ICW*) in kg is calculated as 78% of BCM This is the mean result of two different ways of calculation. ICW is slightly less than 75 % of BCM if the protein content is 25% of the wet weight (*loc cit*) However applying the common assumption that the potassium concentration is 150 mmol per kg/ICW the ICW will be 80% of BCM, calculated as above.

Extracellular water (*ECW*) in kg is calculated as (TBW−ICW) where TBW is the total body water calculated from THO

Body fat (*BF*) in kg is calculated as

$$BW-(BCM+ECW+FFECS)$$

where BW = body weight and FFECS = fat-free extracellular solids approximated to 12 / of BW

Predicted body composition The body weight was predicted from the actual height of the individual, given by Karlberg Iggbom for healthy children (11) The chart in Fig 1 was constructed from the data given by Friis-Hansen (8) allowing prediction of TBW ICW and ECW as per cent of BW at different ages From these figures the predicted values for BCM, K and BF were calculated using the

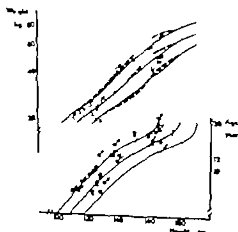


Fig. 2. Body weight in relation to body height (top part of the picture) and body height in relation to age (bottom part of the picture) for 23 subjects with cerebral palsy The data are plotted on the Karlberg Iggbom diagram (11). The lines represent the 97.5, 50 and 2.5 per cent population limits. The dashed line represents girls at differences between girls and boys.

Body height (BH) was recorded in standing position (with due corrections for contractures) In some subjects lying height had to be used The child was placed on the floor with his heels against the wall one or several assistants holding the child fixed as straight as possible Then the longest distance between the wall and the top of the head was recorded In subjects with severe contractures height was measured in a standardized way (22)

Body weight (BW) was recorded on a chair scale (Stathmos-Lindell 822 Jönköping Sweden sensitivity 20 g) The scale was checked regularly and the weighing procedures standardized as far as possible Thus the same assistant weighed each child nude or in pyjamas at the same time of the day usually before bedtime and when the bladder had been emptied

Total exchangeable potassium and total body water were determined by the aid of isotope dilution techniques using ^{42}K and tritiated water (THO) as tracers as described from this laboratory (14) The schedule for administration of the isotopes and collection of urine is outlined in Table 2 Depending on body weight 50–100 μCi ^{42}K and 100–200 μCi THO were given perorally The equilibration period for ^{42}K was about 36 hours and that for THO six hours (for reasons given below) The specific activities (^{42}K/^{39}K and THO/H_2O respectively) were calculated from measurement on two consecutive voidings collected after the equilibration period

The activity of ^{42}K in the urinary samples was measured in a Geiger-Müller liquid counter (type M6 20th Century Electronics Ltd). Stable potassium (^{39}K) was measured in a flame photometer (Eppendorf) after dilution 1:200 with demineralized water

Samples for THO-determination were destilled on a sandbath. Of the colour free destillate 0.50 ml was mixed in duplicate with 10 ml of a scintillation liquid (17) and measured in a liquid scintillation counter (Tri Carb Packard Instruments Co)

The determination of total exchangeable potassium was repeated after one week, sometimes after 2–4 weeks Calculations of the body composition data were based on the mean of these two duplicate determinations

Dietary record The food intake of the subjects was recorded by a trained dietitian who observed the particular subjects during their meals for two separate days The subjects ate in groups at the dinner table in their ward They helped themselves as much as possible Some of them however were in need of some help in serving and/or eating During the meals, the dietitian always played a passive role just recording all items consumed by the subject during the study and estimating the quantities by eye She was quite familiar with the recipes of the dishes and with the relation between size and quantity of the different food items The dietitian also interviewed the subject and the staff concerning any possible extra consumption between meals. The calculation of the intake of energy protein, fat carbohydrate calcium iron vitamin A, thiamin, riboflavin and ascorbic acid was made by aid of food composition tables (1)

TABLE 2 *The schedule for the isotope administrations and collection of urinary samples for analysis*

Time Hours		Urine sampl	Analysis		
0	^{42}K administration	U0			
0–30	Food and water ad l b	U1	^{42}K		THO
30–36	W t no food				
36	THO administration				
36–4	Wat no food	U2	^{42}K	K	
42–45	W ter no food	U3	^{42}K	K	THO
45–48	W t +sandwich	U4			THO

Calculations

Body Composition

It is well known that more than 95 of total body potassium is exchangeable and thus equilibrates with labelled potassium (16) The equilibration is complete after 36 hours, i e the specific activity is the same in all parts of the body It is thus possible to calculate the total exchangeable potassium (K) from the specific

TABLE 3 Body Composition Data. *The data actually found in the first line and with the predicted values in the second line*

Index No	Age years	BH cm	BW kg	K_e mmol	TBW kg	TBW/BCM	ECW/BCM	BF/BCM
Spastic subjects								
1	11	139	42.5	1299	22.9	2.15	1.34	1.12
			33	1750	19.5	1.25	0.56	0.41
2	16	160	56.5	2419	33.7	1.67	0.89	0.57
			47	2700	29.8	1.21	0.43	0.31
4	21	166	68	2914	40.1	1.94	0.94	0.69
			62	2950	32.5	1.33	0.53	0.37
6*)	10	125	21	868	14.5	2.05	1.31	0.75
			24	1300	14.5	1.23	0.55	0.41
7	9	121	25	1034	17.6	2.06	1.27	0.29
			22.5	1200	13.6	1.24	0.58	0.42
8*)	15	165	44	2047	31.5	1.86	1.09	0.21
			44	2700	31.0	1.38	0.60	0.51
11	13	140	40	1603	22.0	1.64	0.96	0.77
			32	1750	19.5	1.24	0.56	0.30
14	14	137	36.5	1805	25.7	1.82	1.16	0.25
			30	1700	18.8	1.22	0.54	0.45
15	17	164	47	2366	35.0	1.78	1.00	0.11
			52	3000	33.0	1.30	0.52	0.22
17	15	135	51	1197	19.3	1.93	1.15	2.34
			29	1600	17.7	1.31	0.53	0.36
20	12	137	32.5	1424	(16.1)[b]	(1.68)[b]	0.81	0.66
			26	1400	16.2	1.32	0.44	0.26
12*)	8	126	24.5	1201	16.6	1.54	0.78	0.39
			24.5	1250	15.2	1.35	0.57	0.28
22*)	7	122	22.5	1129	16.5	1.75	0.87	0.15
			23	1250	14.2	1.25	0.57	0.28
24	8	131	25	1211	20.1	1.99	1.21	0.33
			26.5	1400	16.4	1.38	0.67	0.34
25	8	118	22	882	13.7	1.85	1.07	0.64
			20.5	1140	12.7	1.35	0.58	0.34
26	7	114	21	885	15.3	1.96	1.19	0.33
			20	1100	12.4	1.26	0.57	0.34
Dyslectic subjects								
9	14	158	49.5	2810	35.7	1.84	0.86	0.14
			53	3000	33.0	1.22	0.54	0.30
16	18	166	49.8	2559	33.6	1.84	1.06	0.62
			55	3190	34.5	1.23	0.65	0.24
19*)	17	160	61.6	2230	31.5	1.69	0.91	0.52
			40.6	1850	22.2	1.44	0.67	0.64
18	12	136	28.5	1301	21.1	1.35	1.18	0.16
			29	1600	17.7	1.31	0.43	0.26
21*)	9	126	20.5	915	14.7	1.84	1.14	0.25
			23.5	1400	15.9	1.35	0.57	0.24
27	7	128	26	1510	19.6	1.56	1.09	0.16
			.5	1420	18.8	1.24	0.66	0.24
28	7	110	20	824	14.8	1.90	1.12	0.14
			18.5	1600	11.5	1.24	0.66	0.24
		Mean	36	1561	23.4	1.83	1.06	—
			33	1616	20.2	1.24	0.56	0.25

*) Girls.
b) Determination [illegible]

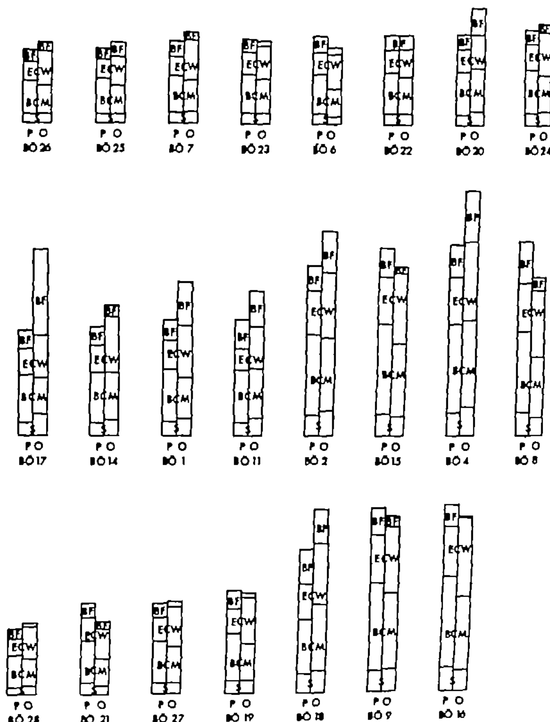


Fig. 3. Individual body composition of the 23 subjects. P — predicted, O — observed, S — fat free extracellular solids, BCM — body cell mass, ECW — extracellular water and BF — body fat. Figures for the 16 spastic subjects are given in the first and second rows, and for the 7 dyskinetic subjects in the third row

same factors and equations as above. BF values within ± 2 S.D. of the mean predicted value for the total material (less the two post pubertal girls) were considered normal. This range was 0.26–0.44 kg BF per kg BCM. Those above this range were called obese and those below slender.

Statistical treatment of the body composition data was limited to an analysis with the sign test which is a qualitative test of a change or a deviation outside an initial observation or from a normal value. The fraction of changes in one direction of the total number of observations gives the level of significance. Significant changes can then be quantitatively defined with the mean value and the standard deviation or standard error.

Table 5 *Predicted energy requirements uncorrected* ($kcal_{pred}$) *and corrected for abnormal Ke* ($kcal^{corr}_{pred}$) *and actual intake calculated for 2 day-records in 30 subjects with cerebral palsy*

Subject No.	Predicted energy requirement $kcal_{pred}$	$kcal^{corr}_{pred}$	Actual energy intake kcal	in % of $kcal^{corr}_{pred}$	Estimated activity¹)
Spastics					
1	2200	1650	945	58	–
2	2250	2100	1212	58	–
4	2650	2500	3296	131	N
6	1550	1000	1409	141	+
7	1600	1550	1489	96	+
8	2300	1750	1751	100	+
11	2250	2050	1601	78	–
14	1800	1700	1524	90	+
16	2400	2050	1878	92	+
17	2000	2400	1617	67	–
K.L.	2200	–	1831	–	
P.A.	1450	–	1539	–	
13	1350	–	1451	–	
20	1750	1800	1418	79	–
22	1950	1800	1236	69	–
23	1850	1650	1335	80	N+
24	2100	1750	1640	93	+
25	1650	1300	1306	100	–
26	1800	1450	1291	89	N
Dyskinetics					
9	3100	2700	1189	44	N+
16	2660	2150	2415	113	+
I.J.	2650	–	2030	–	
J.E.	2000	–	1600	–	
10	1750	–	1791	–	
12	2150		1680	–	
18	1700	2060	1822	90	N
19	2080	1680	1616	96	+
21	2060	1380	1674	124	+
27	2060	1760	1107	63	N+
28	1600	1350	1479	110	+

¹) indicates increased activity, N normal, – decreased, and N+ normal or increased activity

a mean of 1.85±0.02 (S.E.). ECW expressed in kg per kg BCM was increased from the predicted 0.56±0.01 (S.E.) to 1.06±0.03 (S.E.).

BF expressed in terms of kg per kg BCM was increased in 7 of the spastic subjects and reduced in 5. None of the dyskinetic subjects showed an increase and 6 were slender.

Nutrition

The *nutritional value of the diet* consumed between November 1966 and February 1967 is seen in Table 4, where the mean figures from 39 different daily dietary records are given in relation to energy content and compared with a recommendation for the age-groups 10–22

Nutrition

The *nutritive value* of the diet consumed November 1966–February 1967 was evaluated *from its mean content of nutrients per 1000 kcal* based on 10 two-day records and 1 one-day record using the norm of the Swedish Institute for Public Health (21) as reference

Predicted energy requirement ($kcal_{pred}$) was calculated for each child from age sex predicted BW and the figures of Hansen (9) for estimated energy needs in kcal/kg × day From the relation of actual K to predicted K a *corrected predicted energy requirement* ($kcal^{corr}_{pred}$) could be calculated

Predicted "recommended dietary allowances for protein calcium iron vitamin A and ascorbic acid were taken from the table in Recommended Dietary Allowances 1968 (7) For thiamin it was calculated as 0.5 mg per 1000 kcal (*loc cit*) and for riboflavin as k $BW^{0.75}_{pred}$ where k is 0 09 in the age group 10–12 0 08 in 12–14 and 0 07 in ages above 14 (*loc cit*)

Results

Body height and weight

Fig 2 shows body weight (BW) in relation to body height (BH) recorded on the Karlberg Lggbom growth diagram (11) for the 23 subjects Fig 2 also shows the body height in relation to age

The students were generally short with 18 subjects at or below the 50 per cent population limit for age and with 7 even below the 2.5 per cent population limit None had a height above the 97.5% population limit. The mean retardation of height was 7 7±1.5 cm (S.E.). The height retardation of subjects 10–21 years old was 10 6±1 6 cm (S E) while the children between 7 and 9 (Nos 22–28) had a mean retardation of 3 0±2.3 cm (S E.)

Weight in relation to height revealed the preponderance of heavy boys Out of 17 boys 4 were above the 97.5 % population limit and none was below the 2.5 % population limit The 6 girls showed a more normal weight distribution

Body composition

Table 3 and Fig 3 show the body composition of the subjects with the observed and predicted values The deviation from predictions of the observed K and TBW in absolute amounts and of TBW and ECW per kg BCM are statistically significant ($p < 0.01$) Compared with predicted values the observed K (BCM and ICW) was reduced to a mean of 85 7±2.5* (S.E.). Increased K was found only in one subject (No 18) Observed TBW was increased to a mean of 115 0±2.5° (S E) of the predicted. TBW in kg per kg BCM was increased from the mean predicted value of 1 34±0 01 (S.E) to

TABLE 4 *Mean content of nutrients per 1000 kcal in the Bräcke Östergård diet November 1966–February 196 calculated from 39 individual records collected during 12 different days on 19 subjects compared with the recommendations of the Swedish Institute of Public Health for the age groups 10–22 years (21)*

Nutrient	Institutional diet Mean and S.D per 1000 kcal	Recommended (ref 21) 10–2? years	Number of subjects below recommendations n = 19
Protein g	36 ± 4 8	≥29	0
Fat g	4 ± 5 1	≤33	16[a])
Calcium g	0 73 ± 0 [illegible]	≥ 0 67	3
Iron mg	4.9 ± 1 5	≥ 9	19
Vitamin A IE	13[illegible]0 ± 80	≥1500	14
Thiamin mg	0.5 ± 0 17	≥ 0.5	5
Riboflavin mg	1 17 ± 0 [illegible]	≥ 0 75	2
Ascorbic acid mg	37 ± [illegible]0	≥28	8

[a]) The figure for fat denotes number of subjects above the recommended content

TABLE 5 *Predicted energy requirements uncorrected ($kcal_{pred}$) and corrected for abnormal Ke ($kcal^{corr}_{pred}$) and actual intake calculated for 2 day-records in 30 subjects with cerebral palsy*

Subject No.	Predicted energy requirement		Actual energy intake		Estimated activity[1])
	$kcal_{pred}$	$kcal^{corr}_{pred}$	kcal	in % of $kcal^{corr}_{pred}$	
Spastics					
1	2200	1650	948	58	–
2	2340	2100	1212	58	–
4	2650	1800	2393	131	N
6	1450	1000	1409	141	+
7	1600	1450	1389	96	+
8	2200	1750	1751	100	+
11	2250	2050	1601	78	–
14	1900	1700	1524	90	+
15	2400	2050	1878	92	+
17	2000	1500	1017	67	–
K.L.	2300	–	1831	–	
P.A	1450		1539	–	
13	1350	–	1461	–	
20	1750	1800	1418	79	–
21	1950	1600	1279	80	–
23	1840	1650	1328	80	N+
24	2100	1750	1440	82	+
25	1650	1300	1308	100	–
26	1600	1450	1291	89	N
Dyskinetics					
9	3100	2700	1190	44	N+
14	2650	2150	2418	113	+
I.J	2850	–	3050	–	
J.E	2000	–	1600	–	
10	1750	–	1791	–	
12	2150	–	1680	–	
18	1700	2050	1823	89	N
19	2050	1650	1618	98	+
21	2050	1350	1674	124	+
27	2040	1750	1107	63	N+
28	1600	1340	1470	110	+

[1]) + indicates increased activity, N normal, – decreased, and N+ normal or increased activity

mean of 1.85±0.03 (S.E.). ECW expressed in kg per kg BCM was increased from the predicted 0.86±0.01 (S.E.) to 1.06±0.03 (S.E.).

BF expressed in terms of kg per kg BCM was increased in 7 of the spastic subjects and reduced in 5. None of the dyskinetic subjects showed an increase and 6 were slender.

Nutrition

The *nutritional value of the diet* consumed between November 1966 and February 1967 is seen in Table 4, where the mean figures from 39 different daily dietary records are given in relation to energy content and compared with a recommendation for the age-groups 10–22

TABLE 6 *Daily intake of some nutrients calculated from 19 two-day records and 1 one-day record in 19 subjects with cerebral palsy studied November 1966–February 1967*
Underlined data indicates an intake below recommended allowance (7)

Subject No	Protein g	Calcium g	Iron mg	Vitamin A I.E.	Thiamin mg	Riboflavin mg	Ascorbic acid mg
Spastics							
1	35	0.5	5 9	_540	0 6	0 7	41
	4	1 0	7 7	1220	0 7	1.5	40
4	134	_8	14 1	4430	1 7	3.8	68
6	51	1.3	5 7	1410	0 7	—	33
	54	1.3	6 0	1320	1.0	2_	45
8	71	1 6	8.5	1860	1 2	2.4	53
11	53	1.3	5 7	1700	0 8	1 8	29
13	44	0 8	6.2	1740	0 8	1 4	1 1
14	45	0 8	7 5	4550	1 0	1.8	93
15	78	1.3	16 1	15100	1 4	3.6	94
17	36	0 5	6 1	2320	0 6	0 7	35
K L.	57	1.3	7 9	1190	0 9	1	44
P.A	51	1 1	5 6	1620	0 7	1 8	31
Dyskinetics							
9	46	1_	3 2	1490	0 6	1 6	12
10	71	1 7	8.5	1750	1 3	2 8	48
1	67	1	8 0	1410	1 0	1 9	86
16	110	1 5	19.3	15300	2.8	4 7	134
I.J	83	1.5	8 9	2150	1 2	2.3	139
J E	6	1 4	6 1	1760	0 9	2.0	46

years of the Swedish Institute of Public Health (21) The institutional diet had a much lower iron content than recommended an insufficient content of vitamin A and a fat percentage which was too high In other nutritional respects it could be regarded as satisfactory for healthy and active children The last column in Table 4 shows however that the subjects often took their choice between the different food items in such a way that the resulting nutritional quality was below the recommendations in one or several respects Only the protein percentage was at an acceptable level in all subjects when expressed per energy unit.

Table 5 shows the *energy intake* for each subject as the mean for the two days measured The actual intake can be compared with a requirement predicted for a child of the same height but with normal body weight and composition. All except 5 of the 30 subjects studied consumed less calories than predicted When due regard was taken to the reduced K by calculating $kcal^{corr}_{pred}$ (which was not possible for Subjects 10 12 13 K.L. P.A I.J and J E) 9 subjects showed a lower actual intake while 3 seemed to consume more The remaining 11 subjects consumed 80–113 per cent of the predicted value

The individual intake of some *nutrients* is given in Table 6 Data for Nos 18–28 are not given here as the institutional diet had been extensively improved according to the experimental design, when these subjects were studied

Underlined data represent intake below the recommended values calculated as described above. The absolute amount of protein consumed was lower than recommended for the particular subject in 4 of the 19 subjects, of calcium in 7 iron in 17 vitamin A in 13 thiamin in 6 riboflavin in 9 and ascorbic acid in 7 subjects.

Discussion

The determination of the body composition with isotope dilution methods is definitely better than densitometric and anthropometric methods as it allows for direct measurement of different body compartments. Our laboratory has a long experience in isotope dilution methods, and the errors inherent in such methods have been extensively studied. The studies have proved that the practical arrangements with peroral ingestions of isotopes, the equilibration times, and the use of urine to determine the specific activity are satisfactory (14) The indirect calculation of ECW agrees well with the result obtained from direct measurement (15) The equations given by Moore *et al* (16) are valid if the intracellular potassium concentration is normal, which is said to be the case even in extreme pathological disturbances (16)

The result of the body composition studies has been given in absolute figures and also per unit BCM. In this material, the latter expressions give a more clear picture of the changes in the cellular environment than those related to BW as all deviations in different compartments influence the body weight. The body cell mass represent the metabolic body size Other compartments of the body can be considered as service organs to the active mass as a storage of energy as transport mediums and as supports

The material is small and represents a selected sample of severely handicapped subjects. It was thus not possible to conclude that the deviations had normal distribution. Therefore we did not consider it correct to apply other statistical method than the sign test

The intake of energy and nutrients was calculated from a two-day record for each subject. This is a very small number of observations and demands caution in the interpretation of the data However most of the subjects have been studied several times during the subsequent longitudinal studies which will be reported elsewhere (2) The dietary recordings during these later studies regularly comprised 3–12 days mean 7 days in 53 subject periods. A comparison between the mean value of the two first observations with the mean of all observations in each subject period gave a methodological error of 8.6% and a range of 29% The mean of these differences for the 53 subject periods was just – 30 kcal. It thus seemed justifiable to regard the results obtained in the present study as representative for the energy intake of the subjects.

The short stature of our subjects is in conformity with what has been found in other materials reported previously (4 5 10 13 20 22) Sterling (20) compared the height of 100 children with that of their healthy siblings and found that 69 % of the patients and only 4% of the siblings were below the 10 percentile Weights were found to vary more than heights, but generally the children were lighter than expected considering their age Our material *indicates that the* growth-retarded child with cerebral palsy often has a weight which is normal or increased considering its height an observation which has not been stressed in the papers mentioned above

To our knowledge body composition studies of children with cerebral palsy have not been reported previously In a cerebral palsy material, an abnormal body composition can be expected In our material, the composition showed some surprisingly great deviations from the predicted values. However the low BCM observed in most subjects was in agreement with the condition of the subjects. In normals the muscle mass comprises more than 70 per cent of the BCM In children with cerebral palsy the muscle development can be *retarded* for three reasons: low physical activity malnutrition and paresis of muscle groups Of particular interest, however is the *fact that* the physically more active

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Underlined data indicates an intake below recommended allowance (7)

Subject No	Protein g	Calcium g	Iron mg	Vitamin A I.E.	Thiamin mg	Riboflavin mg	Ascorbic acid mg
Spastics							
1	35	0.5	5.9	_540	0.6	0.7	41
	42	1.0	7.7	1220	0.7	1.5	40
4	124	2.8	14.1	4430	1.7	3.8	68
6	51	1.3	5.7	1410	0.7	—	23
7	54	1.3	6.0	13*0	1.0	2.2	45
8	71	1.6	8.5	1860	1.2	_4	53
11	53	1.3	5.7	1700	0.8	1.8	29
13	44	0.8	6._	1740	0.8	1.4	121
14	45	0.8	7.5	4550	1.0	1.8	93
15	78	1.3	16.1	15100	1.4	3.6	94
17	36	0.5	6.1	2320	0.6	0.7	25
K.L.	57	1.3	7.9	1100	0.9	2.1	22
P.A.	51	1.1	5.6	1620	0.7	1.8	2[illegible]
Dyskinetics							
9	46	1._	3.2	1490	0.6	1.6	12
10	71	1.7	8.5	1750	1.3	_8	48
12	67	1.2	8.0	1410	1.0	1.9	86
16	110	1.5	10.3	15300	2.8	4.7	134
I.J	83	1.5	8.0	2150	1._	2.3	139
J E	6	1.4	6.1	1780	0.9	_0	46

years of the Swedish Institute of Public Health (21) The institutional diet had a much lower iron content than recommended an insufficient content of vitamin A and a fat percentage which was too high In other nutritional respects it could be regarded as satisfactory for healthy and active children The last column in Table 4 shows however that the subjects often took their choice between the different food items in such a way that the resulting nutritional quality was below the recommendations in one or several respects. Only the protein percentage was at an acceptable level in all subjects when expressed per energy unit.

Table 5 shows the *energy intake* for each subject as the mean for the two days measured The actual intake can be compared with a requirement predicted for a child of the same height but with normal body weight and composition All except 5 of the 30 subjects studied consumed less calories than predicted. When due regard was taken to the reduced K by calculating $kcal^{corr}_{pred}$ (which was not possible for Subjects 10 12 13 K L P.A I J and J E) 9 subjects showed a lower actual intake while 3 seemed to consume more The remaining 11 subjects consumed 89–113 per cent of the predicted value

The individual intake of some *nutrients* is given in Table 6 Data for Nos 18–28 are not given here as the institutional diet had been extensively improved according to the experimental design when those subjects were studied

the use at the Centre of the old Autenrieth method to determine hemoglobin as acid hematin Two years later the subjects were studied with a more accurate method (oxy hemoglobin) by trained technicians. Several subjects were then found to have low hemoglobin values, as well as low serum iron and high transferrin levels

It is not known if the low physical activity per se can cause deviations in the body com position of the type found here As the present study could not give an answer to the question of the role played by poor nutrition and low physical activity for the body composition in subjects with cerebral palsy a longitudinal study was started for further penetration of these problems.

Summary

Height weight, body composition, and intake of energy and of som essential nutrients were determined on 22 full board subjects with cerebral palsy aged 7 21 years, from Bräcke Östergård Pediatric Habilitation Centre

Body height was generally small for age while weight often was increased for height

The mean body cell mass was 86 per cent of the value predicted for height

The extracellular water was strikingly in creased in all subjects

Body fat was increased in 7 spastics and reduced in 5 spast cs and in 6 of the 7 dyskinetics

The observed energy intake was low but adequate for active met bolic mass in 11 of 22 subjects. The reduced energy requirements of most subjects resulted n an insufficient supply of several essential nutrient due to the composition of the food offered.

Low physical activity and malnutrition were suggested as possible causes of the abnormal body composition.

Acknowledgement

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dyskinetic subjects also showed a reduced BCM with one exception

Absolute or relative changes in ECW are common in unhealthy subjects (10) The strikingly abnormal increase in ECW in the present *material was unexpected however All subjects* were healthy with respect to the cardio-vascular system the liver the kidney and the endocrines *In wasting of a disease the reduction* of body cell mass favours the increase in extra cellular water In our material however the *children cannot be considered to have a wasting* disease but a retardation of the body cell mass development during growth The actual ECW was enlarged to a mean of *158.3±4.5* (*S E*) of a value predicted from the height of a normal child The abnormality is close to what is seen *in severe malnutrition of children (6)*

The overweight seen in this material was to a great extent due to the increased ECW In 7 spastic subjects there was a concomitant increase in the BF On the other hand all dyskinetics and nearly half of the spastics showed a *reduced BF* indicating an insufficient energy intake

For several reasons it is difficult to estimate the energy requirement of handicapped subjects First of all even in normals the energy re*quirement may be expected to vary considerably* and the recommended allowances can only be regarded as mean figures for large groups Due to the abnormal BH and BW of our subjects no comparison was made between their energy intake and the recommended allowances for the same age groups Due to the abnormal body composition of our subjects *it was also regarded* as useless to express their energy intake in terms of kcal per kg BW The ways chosen for the estimations *of the predicted energy require*ment uncorrected and corrected for actual K was regarded as the only possible ones to obtain some references *In this respect it seemed logical* to use the Karlberg Iggbom chart (11) and the data of Hansen (9) for kcal/kg BW A compari*son between* the uncorrected predicted energy requirement and the actual energy intake indicated that practically all subjects had a reduced intake From a comparison between actual energy intake and the corrected predicted energy requirement it was apparent that in most cases the reduced BCM was the main reason for the reduced energy intake Some subjects still showed a pronounced reduction in energy intake Three subjects consumed more than predicted A reduced energy intake in cerebral palsy has been reported in several previous papers (*4 5* 10 12 13) but due regard to the reduced metabolic body size does not seem to have been taken in the interpretation of these results.

These data and the abnormal BF allow some conclusion as to the degree of physical activity An increased body fat mass *in* spite of a low energy intake must mean that there was severe reduction in physical activity On the other *hand* as seen in the dyskinetics and in some spastics a reduced BF in combination with an energy intake normal for the actual BCM should indicate an increased physical activity see last column in Table 5

It can be concluded from a nutritional point of view *that the institutional diet* was *not* suitable for the full board students Its content of nutrients per unit energy was in some respects *well above the recommended values for* healthy children at corresponding ages It was *on the borderline for thiamin and it could not* give a sufficient supply *of iron if the children* did not have an energy requirement well above that of moderately active healthy children The *high protein fat calcium and riboflavin content* stresses the preference for milk and milk containing dishes The bread consumption was *rather low and so was that of meat* and fish with the exception for fat rich sausages Vegetables also played a minor role Thus, the re*duced* energy requirement of most subjects resulted in an insufficient supply of several essential nutrients It is impossible to deny that these insufficient intakes can have had something to do with the abnormal body composition found in these subjects. Anaemia was surprisingly not diagnosed in the children at the time of this study This is in contrast to previous reports (*4 5*) The reason may be technical and due to

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Effect of physical activation and of improved nutrition on the body composition of school children with cerebral palsy

by KRISTINA BERG

In a previous article (3) an abnormal body composition in children with cerebral palsy was reported. Its main features were a considerable increase in extracellular water reduced body cell mass, and a fat mass which was increased in 7 and decreased in 5 spastic subjects and in all but one athetotic subject. Inactivity and malnutrition were suggested as relevant causes.

To test if the body composition abnormalities could be decreased the children with cerebral palsy were subjected to physical training in order to increase their activity. Later they also had a diet with a high content of essential nutrients per unit of energy. The effects of these t measures are reported in this article.

Methods

The methods employed to determine and calculate body composition were the same as used in the initial study (3). In the evaluation of the possible effects of training and diet due consideration was taken to all determinations during the period concerned. All predicted values were calculated as described in a previous paper (3).

For activation each child had physical training for three 30-minute periods a week with activities involving large muscle groups and giving a high heart rate during each training session. Method for training and testing and the effects of the training on the physical working capacity are reported separately (1).

During the initial activation period, the institutional diet had the same general composition as outlined in a previous paper (3). Then the menues and recipes were completely revised in order to create a diet with a high content of nutrients per unit of energy sufficient to meet the nutritional needs even for those with a very low energy requirement. The composition of the diet started in September 1967 is given in Table 3.

The *dietary intake* was recorded in the same way as described previously (3). The number of daily records however was increased to 7 (range 3–12) for every subject in each separate study.

General procedure

The general procedure for the different longitudinal studies (A B and C) is outlined in Fig. 1 which shows the daily routine for the subjects and the frequency of experimental observations. After the initial body composition determinations reported in the preceeding article (3) the subjects of *Study A* had hard physical training during the spring of 1967. Then, three months of summer vacation at home followed, which meant inactivation for most subjects. When the subjects returned to school their body composition was rechecked. Then *Study B* started. In addition to the same training program as in Study A, the subjects received the new institutional diet. This study lasted one school year from September 1967 until June 1968. During the following school year additional studies were made on some subjects of Study B. In August 1968 *Study C* with subjects who had not been in the institution

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Fig 1 General procedure f Studies A B and C The frequency of the d fferent determinations and th periods of the different therapies re given.

TABLE I *Participation of the school children with cerebral palsy in the various studies*

Initial determinat ons			Study A		Study B	Studies after Study B	Study C
S bjects	month	yea	Period of physical training	Determination after vacation		(Change in routine)	
1	10 11	1966	×	×	×	×	
	9	1967			×	× (tendon operation)	
4	10, 11	1966	×	×	×	×	
6	12	1966					×
7	12	1966	×	×	×	× (training)	
8	1 1	1966–67	×	×	×	(severe illness)	
0	1	1967	×	left			
11	1	1967	×	×	×	× (tendon operation)	
14	1	1967	×	×	×	×	
15	1	1967	×	×	×	(left)	
16	1	1967	×	×	×	×	
1		1967					×
18	9	1967			×	× (no training)	
19	9	1967			×	(left)	
20	9 10	1967			×	× (no training)	
1	9	1967			×	(no tra ning)	
22	9	1968					left
23	9	1968					×
4	9	1968					×
25	9	1968					×
26	9	1968					×
27	0	1968					×
28	9	1968					×

during the previous year was started. These subjects were given the new institutional diet but had no physical training. On the other hand their spontaneous activity was not restricted. This study lasted also for one school year until June 1969.

Material

The material consisted of 22 of the 23 subjects whose initial body composition data were reported previously (3). The excluded subject (N 22) left the institution after only 3 months. As seen in Table 1 nine subjects participated in Study A, 13 in Study B (8 subjects from Study A), 10 of these in the study following Study B and 8 new subjects in Study C. In the studies following Study B only four subjects continued their physical training (Nos. 1, 4, 14 and 16). The daily routine for the other subjects was affected in different ways as shown in Table 1.

Results

The *physical training* during Studies A and B resulted in an increase in the maximal oxygen uptake as reported separately (1).

The *energy intake* (Table 2) was not recorded during Study A. As a whole the energy intake in Study B was higher than before Study A in 7 of the 9 subjects for whom data were available. During the studies following Study B 4 of 8 subjects seemed to reduce their energy intake — even of the 4 subjects who continued the training program. The new subjects in Study C showed a small increase when the June 1969 values were compared with the November 1968 ones. The difference was so small, however, that the figures given in Table represent mean figures for all records during the study. In Study B, 6 of the 13 subject consumed 85–115 per cent of $kcal^{corr}_{pred}$ (2), 5 were below and 2 above that range. The corresponding figures for the 8 subjects in Study C were 6, 1 (+1) and 0 respectively.

The food selected by the subjects usually had a somewhat lower *content of nutrients per 1000 kcal* than the diet offered, but was satisfactory in most respects during Studies B and C (Table 3). The iron content was insufficient for the girls.

The *individual intake of some nutrients* is given in Table 4. Underlined data represent intake below the recommended values, calculated as

TABLE 2. *Predicted energy requirements corrected for abnormal Ke* ($kcal^{corr}_{pred}$) *and mean actual intake calculated for daily non-consecutive records in Study B, in the additional study after Study B and in Study C* (*No. of records see Table 4*)

Subject No.	Predicted energy requirement $kcal^{corr}_{pred}$	Mean actual energy intake in kcal	Mean actual energy intake in % of $kcal^{corr}_{pred}$
Study B			
1	1900	1612	95
2	2150	1350	63
4	2780	437	69
7	1600	1586	99
8	2300	1847	80
11	2000	1528	76
14	1850	1622	88
15	2300	2164	94
16	2600	2940	113
18	2480	1627	66
19	1550	2047	132
20	1650	1353	84
21	1250	1591	127
Study after Study B			
1	2500	1160	46
7	1700	1061	62
11	2150	1351	63
14	1750	1671	95
16	2750	3677	134
18	2450	1770	72
20	1580	1062	67
21	1–50	1514	121
Study C			
6	1150	1140	99
17	1500	(980+)*	(65+)*
23	1700	1334	78
24	2150	1933	90
25	1330	1434	108
26	1550	1491	96
27	1580	1350	85
28	1400	1554	111

*) Habitually great intake of sweets.

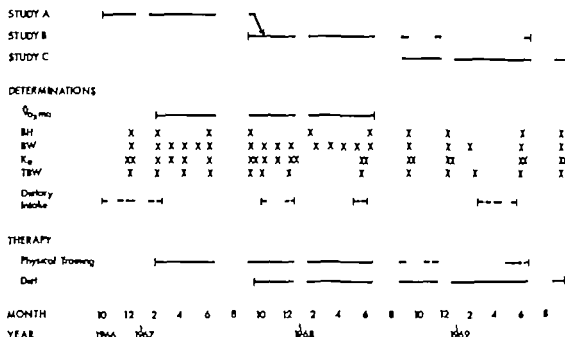


Fig 1 General proced ro f r Studies A B and C The frequency of the d fferent determinations and the periods of the diff rent therapies are gi en.

TABLE 1 *Participation of the school chil lren with cerebral palsy in the various studies*

Init al determinations			Study A		Study B	Studies after Study B	Study C
Subject	month	year	Period f physical trai ing	Determination ft r vacation		(Change i routine)	
1	10 11	1966	×	×	×	×	
	9	1967			×	× (tendon operation)	
4	10 11	1966	×	×	×	×	
6	1	1966					×
7	1	1966	×	×	×	× (no training)	
8	1 1	1966–67	×	×	×	(severe illness)	
9	1	1967	×	left			
11	1	1967	×	×	×	× (tendon operation)	
14	1	1967	×	×	×	×	
15	1	1967	×	×	×	(left)	
16	1	1967	×	×	×	×	
17		1967					×
18	9	1967			×	× (no tra ning)	
19	9	1967			×	(left)	
[illegible]0	9 10	1967			×	× (n train ng)	
1	9	1967			×	× (no training)	
[illegible]	9	1968					left
23	9	1968					×
4	9	1968					×
3	9	1968					×
26	9	1968					×
[illegible]7	9	1968					×
28	9	1968					×

during the previous year was started. These subjects were given the new institutional diet but had no physical training. On the other hand their spontaneous acti ty was not restricted. This study lasted also for one school year until June 1969.

Material

The material consisted of 22 of the 23 subjects whose initial body composition data were reported previously (3). The excluded subject (No 22) left the institution after only 3 months. As seen in Table 1 nine subjects participated in Study A, 13 in Study B (8 subjects from Study A), 10 of these in the study following Study B and 8 new subjects in Study C. In the studies following Study B only four subjects continued their physical training (Nos. 1 4 14 and 16). The daily routine for the other subjects as affected in different ways as shown in T ble 1.

Results

The *physical train ng* during Studies A and B resulted in an increase in the maximal oxygen uptake as reported separately (1).

The *energy intake* (T ble 2) was not recorded during Study A. As a whole the energy intake in Study B was higher than before Study A in 7 of the 9 subjects for whom data were available. During the studies following Study B 4 of 8 subjects seemed to reduce their energy intake — even 2 of the 4 subjects who continued the training program. The new subjects in Study C showed a small increase when the June 1969 values were compared with the November 1968 ones. The difference was so small, however that the figures given in Table 2 represent mean figures for ll records during the study. In Study B 6 of the 13 subjects consumed 85–115 per cent of $kcal^{corr}_{pred}$ (3) 5 were below and above that range. The corresponding figures for the 8 subjects in Study C were 8 1 (+1), and 0 respectively.

The food selected by the subjects usually had somewhat lower *content of n trients per 1000 kcal* than the diet offered, but was satisfactory in most respects during Studies B and C (Table 3). The iron content was insufficient for the girls.

The *individual intake of some nutrients is given* in Table 4. Underlined data represent intake below the recommended values calculated as

TABLE 2. *Predicted energy requirements corrected for abnormal K ($kcal^{corr}_{pred}$) and mean actual intake calculated for daily non-consecut ve records in Study B in the additional study after Study B and in Study C (N of records see Table 4)*

Subject K	Predicted energy requirement $kcal^{corr}_{pred}$	Mean actual energy intake in kcal	in % of $kcal^{corr}_{pred}$
Study B			
1	1900	1812	95
2	2150	1359	63
4	2750	2437	89
7	1400	1466	99
8	2300	1847	80
11	2000	1528	76
14	1850	1622	88
15	2300	2166	94
16	2600	2940	113
18	2450	1627	66
19	1880	2047	112
20	1680	1383	84
21	1280	1891	157
Study after Study B			
1	2500	1160	46
7	1700	1061	63
11	2150	1351	63
14	1750	1671	95
16	2750	3677	134
18	2450	1770	73
20	1540	1032	67
21	1250	1514	121
Study C			
6	1150	1140	99
17	1500	(960 +)[a]	(65 +)[a]
23	1700	1354	79
24	2150	1922	90
25	1350	1436	106
26	1560	1491	96
27	1850	1580	85
28	1400	1584	113

[a]) Habitually great intake of sweets.

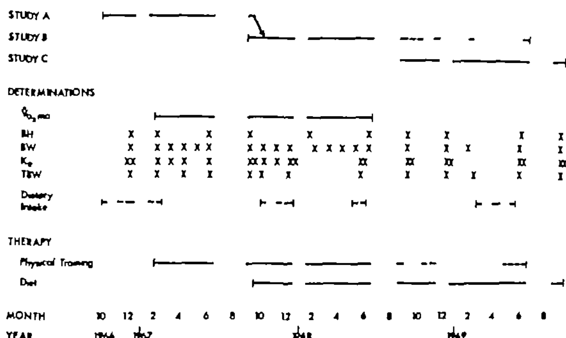


Fig 1 General procedure f r Studies A, B nd C The frequency of the different determination and the period of the d ff rent therapies re given

TABLE 1 *Participation of the school children with cerebral palsy in the various studies*

	Initial determination		Study A		Study B	Studies after Study B	Study C
Subjects	month	year	Period of physical training	Determination after vacation		(Change in routine)	
1	10 11	1966	×	×	×	×	
	9	1967			×	× (tendon peration)	
4	10 11	1966	×	×	×	×	
6	1	1966					×
7	12	1966	×	×	×	× (no training)	
8	1 -1	1966–67	×	×	×	(severe illness)	
9	1	1967	×	left			
11	1	1967	×	×	×	× (tendon peration)	
14	1	1967	×	×	×	×	
15	1	1967	×	×	×	(left)	
16	1	1967	×	×	×	×	
17		1967					×
18	9	1967			×	× (no training)	
19	9	1967			×	(left)	
20	9 10	1967			×	× (no training)	
21	9	1967			×	× (no training)	
22	9	1968					left
23	9	1968					×
24	9	1968					×
25	9	1968					×
26	9	1968					×
27	9	1968					×
28	9	1968					×

TABLE 4 *Mean daily intake of some nutrients calculated from daily non-consecutive records in Study B the additional study following Study B and Study C Underlined data indicates an intake below recommended allowance (6).*

Subject No	Protein g	Calcium g	Iron mg	Vitamin A I.U.	Thiamin mg	Ribo-flavin mg	Ascorbic acid mg	No. of records
Study B								
1	82	1.1	12.8	3450	1.5	2.2	83	7
2	61	0.6	10.3	3750	1.0	1.3	60	7
4	118	1.8	17.0	4580	1.9	3.3	152	7
7	83	1.3	18.7	9200	1.6	3.5	93	7
8	70	0.7	11.9	1300	1.6	1.4	80	7
11	65	0.8	11.2	2500	1.2	1.3	72	7
14	62	0.8	11.7	2840	1.3	1.7	99	7
15	88	1.4	17.3	9350	1.7	3.2	100	7
16	126	1.4	27.4	17300	2.5	4.6	184	7
18	75	1.2	10.9	3750	1.4	2.2	94	7
19	90	1.3	18.8	4750	1.7	2.8	75	7
20	82	1.2	11.4	3100	1.3	3.0	83	7
21	74	1.0	11.3	1200	1.5	2.3	66	7
Study after Study B								
1	66	0.8	6.9	2980	1.0	1.6	157	4
7	47	0.8	6.6	3750	0.8	1.6	26	5
11	66	1.0	8.2	1750	0.8	1.8	40	5
14	62	0.7	9.1	3060	1.2	1.7	237	4
16	147	1.4	28.4	2300	2.5	2.3	78	3
18	67	0.8	10.2	2240	1.3	1.7	166	4
20	84	0.9	8.2	4650	0.9	2.1	43	3
21	78	1.1	11.5	2490	1.7	2.6	83	4
Study C								
8	88	1.3	7.7	4840	1.0	2.8	47	3
17	46	0.9	4.9	1480	0.7	1.3	183	4
23	67	1.0	10.0	1900	0.8	1.7	95	11
24	88	1.6	18.6	1840	1.2	2.4	120	10
28	63	1.0	11.8	2400	1.0	2.0	108	12
35	84	1.1	12.2	3400	1.8	2.1	98	11
37	72	1.3	14.4	3050	1.0	2.3	111	12
39	75	1.3	13.4	3180	1.1	2.2	90	12

TABLE 3 *Mean content of nutrients per 1000 kcal in the Brücke Östergård diet from Sept 196˜ re commended content for healthy subjects between 10–22 years (10) and number of subjects choosing a diet with a content lower than recommended in the different studies*

	Institutional diet	Recommended (10– yrs)	Number of subject below) recommendations Study B n=13	Study fter Study B n=8	Study C n=8
Protein g	5	≥28	0	0	0
F t g	˜9	≤38	1)	˜)	(⁰)
Calcium g	0 78	≥ 0 57	4	3	0
Iron mg	7 8	≥ 7(9)¹)	0(3)²)	4(2)²)	1(1)²)
Vit min A IE	450	≥1500		3	
Thiamin mg	0 91	≥ 0.5	0	0	0
Riboflavin mg	1 48	≥ 0 5	0	0	0
Ascorbic acid mg	67	≥˜8	0		0

) The figures for fat denot number of subject above the recommended co tent.
) Figures outsid bra ket refer to boys, those with bra ket t girls.

described in a previous paper (3) In the studies with dietary records all subjects consumed sufficient amounts of protein thiamin and riboflavin The ascorbic acid intake was below recommendations only in 3 subjects in the stu dy following Study B A few subjects in each study had low amounts of vitamin A The calcium intake failed to reach the recommenda tions in RDA (6) for 6 subjects in Study B 6 in the study following B and in 1 subject in Study C The iron intake was insufficient in 6 7 and 2 subjects respectively

Body heights and weights of the subjects at the start and end of the different studies are given in Table 5 In comparison with their previous growth data no growth spurt was seen

Body Composition

Study A The effects of physical training alone on various body compartments are given in Tables 6–9 K (BCM) was not affected more than can be attributed to the increase in BH The subjects showed a mean decrease in TBW of 2 9 kg corresponding to 200 g per kg BCM This decrease was restricted to the ECW During the summer vacation these effects were reversed for most subjects (6 of ‹ available for determination) All subjects also showed a uniform reaction of BF which in creased regardless of the initial state with a mean of 4 3 kg During the summer vacation, the BF was reduced in 6 of the 7 subjects

Study B The effects of physical training and improved nutrition combined are reported in Tables 6 10–12 Still no general effect on K, was observed when expressed in per cent of the predicted values As in Study A there was a reduction in TBW and ECW here for 11 or 13 subjects the mean reduction was 160 g per kg BCM The BF in relation to BCM increased or was fairly unaffected in all subjects except in 3 obese subjects (Nos 11 14 and 20)

The studies following Study B on 10 subjects during one school year showed significant changes only in BF regardless of whether the subjects continued training or not (see Tables 1 6 and 10–12) Six subjects increased their TBW and ECW and 9 showed a decrease in BF The final values indicated an improvement compared with their initial values (3) except for TBW and ECW in subjects Nos 18 and 20 and BF in No 16

Table 4 *Mean daily intake of some nutrients calculated from daily non-consecutive records in Study B the additional study following Study B and Study C Underlined data indicates an intake below recommended allowance (6)*

Subject No	Protein g	Calcium g	Iron mg	Vitamin A I.U.	Thiamin mg	Riboflavin mg	Ascorbic acid mg	No. of records
Study B								
1	82	1.1	12.8	3450	1.5	2.2	83	7
2	61	0.8	10.3	3750	1.0	1.3	60	7
4	118	1.8	17.0	4850	1.9	3.3	152	7
7	83	1.3	16.7	9200	1.6	3.5	92	7
8	70	0.7	11.9	1300	1.5	1.4	69	7
11	65	0.9	11.2	2500	1.2	1.5	72	7
14	62	0.8	11.7	2550	1.3	1.7	90	7
15	96	1.4	17.3	9350	1.7	2.2	100	7
16	124	1.4	27.4	17300	2.5	4.6	164	7
18	78	1.2	10.9	3750	1.4	2.2	84	7
19	90	1.3	12.6	4750	1.7	2.4	75	7
20	62	1.2	11.4	8100	1.3	2.0	83	7
21	74	1.0	11.3	1200	1.5	2.3	65	7
Study after Study B								
1	83	0.8	6.8	2850	1.0	1.6	187	4
7	4	0.8	6.6	3750	0.8	1.6	26	5
11	66	1.0	6.2	1750	0.8	1.6	40	5
14	65	0.7	8.1	3050	1.3	1.7	237	4
16	147	1.4	34.4	2300	2.5	2.9	76	3
18	67	0.8	10.2	2350	1.2	1.7	165	4
20	64	0.9	8.2	6650	0.9	2.1	43	5
21	76	1.1	11.5	3050	1.7	2.5	53	4
Study C								
6	66	1.2	7.7	4550	1.0	2.5	47	5
17	48	0.9	4.9	1460	0.7	1.3	163	4
23	62	1.0	10.0	1900	0.8	1.7	85	11
24	86	1.5	16.6	1680	1.2	2.4	120	10
25	60	1.0	11.8	3400	1.0	2.0	106	12
26	64	1.1	12.2	3400	1.0	2.1	98	11
27	72	1.3	14.4	3050	1.0	2.3	111	12
29	75	1.2	13.4	3150	1.1	2.2	99	12

TABLE 5 *Body height and weight of school children with cerebral palsy Height in cm and weight in kg before and after the different studies*

Index number	Study A start		Study B start		Study B end		Study after Study B end		Study C start		Study C end	
	BH	BW	BH	BW	BH	BW	BH	BW	BH	BW	BH	BW
1	139	42.5	145	45	150	48 9	157	51.5				
			159	61 7	161	54	161	54 0				
4	166	68	167	70	167	1 0	167	61.5				
6									129	4	134	4 1
7	1 1	.5	1 0	27 5	1[illegible]7	[illegible]8.1	128	30				
8	16	44	163	48 6	164	48 7						
9	165	49 5										
11	140	40	145	4 .5	150	38.5	163	44.5				
14	137	36.3	143	40.5	144	37	151	4[illegible].7				
15	164	47	166	54 5	168	52.4						
10	166	49 6	166	50.5	166	53 5	166	51 5				
17									136	43	140	49 3
18			150	51.5	150	48 5	150	50 0				
19			130	[illegible]8.5	141	[illegible]9						
[illegible]0			12[illegible]	32 3	130	3[illegible]7	136	3[illegible]4				
21			128	[illegible]0 6	131	1 1	133	22.9				
23									123	22 6	130	23.8
4									131	28	134	33.4
25									116	[illegible]	119	21.8
26									114	22	1[illegible]0	23.5
27									1[illegible]8	26	131	29 0
28									110	[illegible]0	115	20 4

TABLE 6. *Effect of physical training and better nutrition on exchangeable body potassium in school children with cerebral palsy. Initial value and $100 \times O/P$ after 4 months of training, after 2 months of summer vacation and after 9 months of training and better nutrition in 14 subjects. Additional studies were done one year later. O = Observed value, P = Predicted value*

Index number	K_e mmol[1]) O / P	Start Dec. 1966 Jan. 1967	After training June 1967	After vacation Sept. 1967	After training and better diet June 1968	Additional study June 1969
1	1270 / 1750	73	73	79	79	83
	2485 / 2775	96	—	—	83	81
4	2880 / 2950	98	98	96	107	107
7	1034 / 1200	86	91	91	88	104
8	2074 / 2700	77	80	83	84	—
9	1868 / 3000	86	86	—	—	—
11	1607 / 1780	92	88	84	82	76
14	1596 / 1700	94	96	90	87	93
15	2400 / 3000	80	80	90	80	—
16	1520 / 3100	81	87	93	93	101
18	2233 / 1850	120	—	—	125	124
19	1301 / 1600	81	—	—	74	—
20	1300 / 1400	93	—	—	90	93
21	935 / 1400	67	—	—	63	73

[1]) Dec. 1966–Jan. 1967 Nos. 1, 4–16; Sept. 1967 Nos. 2, 18–21

TABLE 5 *Body height and weight of school children with cerebral palsy Height in cm and weight in kg before and after the different studies*

Index number	Study A start		Study B start		Study B end		Study after Study B, [illegible]nd		Study C start		Study C [illegible]nd	
	BH	BW	BH	BW	BH	BW	BH	BW	BH	BW	BH	BW
1	130	4[illegible].5	145	45	150	48.9	157	51.5				
			159	61.7	161	54.2	161	54.0				
4	166	68	167	70	16[illegible]	71.0	167	61.5				
6									1[illegible]9	4	134	4.1
7	1[illegible]1	25	1[illegible]6	[illegible]7.5	1[illegible]	28.1	1[illegible]3	30.				
8	16	44	163	48.8	164	43.7						
9	165	49.5										
11	140	40	145	4[illegible].5	150	38.5	163	44.5				
14	137	36.3	143	40.5	144	37	151	4[illegible].7				
15	164	47	166	54.5	168	5[illegible]4						
16	166	49.6	166	50.5	166	53.5	166	51.5				
17									136	48	140	49.3
18			150	51.5	150	48.5	150	50.0				
19			136	[illegible]8.5	141	[illegible]9						
[illegible]0			1[illegible]	32.3	130	3[illegible].7	136	3[illegible].4				
[illegible]1			1[illegible]8	[illegible]0.6	131	[illegible]1.1	133	[illegible]2.9				
[illegible]3									1[illegible]3	2[illegible].6	130	23.8
[illegible]4									131	28	134	33.4
25									116	[illegible]3	119	21.8
26									114	22	1[illegible]0	23.5
27									128	[illegible]6	131	29.0
28									110	[illegible]0	115	[illegible]0.4

TABLE 6 *Effect of physical training and better nutrition on exchangeable body potassium in school children with cerebral palsy. Initial value and 100 × O/P after 4 months of training, after 2 months of summer vacation and after 9 months of training and better nutrition in 14 subjects. Additional studies were done one year later. O = Observed value. P = Predicted value.*

Index number	K_e, mmol[1]) O P	Start Dec. 1966 Jan. 1967	After training June 1967	After vacation Sept. 1967	After training and better diet June 1968	Additional study June 1969
1	1270 1760	73	73	79	79	83
2	2483 2775	89	—	—	83	81
4	2680 2950	95	90	88	107	107
7	1934 1900	96	91	91	89	104
8	2076 2100	77	80	83	84	—
9	1688 3000	88	86	—	—	—
11	1607 1750	92	88	84	82	76
14	1[illegible] 1700	94	96	90	87	93
15	2406 3000	80	80	90	80	—
16	1820 3100	91	87	92	93	101
18	2332 1880	120	—	—	126	124
19	1301 1600	81	—	—	74	—
20	1309 1400	93	—	—	90	92
21	935 1400	87	—	—	63	73

[1]) Dec. 1966–Jan. 1967 Nos. 1–16. Sept. 1967 Nos. 2, 18–21.

Table 7 *Effect of physical training on total body water in school children with cerebral palsy Initial values and changes in kg and in TBW/BCM during 4 months of training and 2 months of summer vacation in 9 subjects*

Index number	Initial observation Predicted value Dec 1966 Jan 1967	Change during training	$\frac{TBW^{1})}{BCM}$ at start Dec 1966 Jan 1967	$\frac{TBW^{1})}{BCM}$ at end June 1967	Additional study Change during vacation Sept 1967
1	2_.8 19 5	−3 7	_16	1 80	4.3
4	40 1 3_5	−4 6	1 67	1 48	_5
7	17.3 15 5	0	01	1 70	0.4
8	31 8 31 0	−_5	1.84	1 70	5.
9	35 7 33.0	−3 1	1 66	1 5	—
11	42.8 19 5	−1 4	1 70	1 60	_3
14	5 7 18.5	−3 7	1 93	1 34	−1 1
15	35 2 32.5	−_7	1 75	1 6	)
16	38 6 34 5	−4 6	1 84	1 49	0 1

) Predicted TBW/BCM 1 33±0 01 (S D) for the female subject No 8 1 40

²) Technical failure of determination

TABLE 8 *Effect of physical training on extracellular water in school children with cerebral palsy Initial values and changes in kg and in ECW/BCM during 4 months of training and 2 months of summer vacation in 9 subjects*

Index number	Initial observation Predicted value Dec. 1966 Jan 1967	Change during training	$\frac{ECW}{BCM}$[1] at start Dec 1966 Jan 1967	$\frac{ECW}{BCM}$[1] at end June 1967	Additional study Change during vacation Sept 1967
1	14.8 8.0	2.7	1.27	1.02	−7
4	21.4 13.0	−4.6	0.89	0.79	2.3
7	10.6 5.5	−1.3	1.22	0.91	0.4
8	18.3 13.5	−2.6	1.06	0.81	4.8
9	19.0 13.5	−3.1	0.88	0.74	–
11	12.3 6.0	1.4	0.92	0.81	2.1
14	18.3 .5	0.1	1.18	0.86	2.6
15	18.6 13.0	−2.7	0.94	0.84	[2]
16	22.2 14.3	−4.0	1.08	0.71	−0.8

[1]) Predicted ECW/BCM = 0.54 ± 0.01 (S.D.), and for the female subject No. 8: 0.62.
[2]) Technical failure of determination.

TABLE 9 *Effect of physical training on body fat in school children with cerebral palsy Initial values and changes in kg and in BF/BCM during 4 months of training and 2 months of summer vacation*

Index number	Initial observation Predicted value Dec 1966 Ja 1967	Change 1 ring training	BF[1]) / BCM at start Dec 1966 J n. 1967	BF[1]) / BCM t end June 1967	Additional study Change duri g acation Sept 1967
1	1_3 6.0	3 3	1 10	1 47	—
4	14 4 9 1	7	0 00	0 90	−3 3
7	_8 4 3	1 0	0 33	0 46	−0 6
8	3.3 11 5	6 7	0 19	0.50	−5.5
9	3 1 7 5	4 4	0 14	0 35	
11	9 5 5.7	1 4	0 71	0 81	−0._
14	3 3 5.0	3 7	0 _5	0 43	2.3
15	_1 8 0	5.4	0 11	0 38	)
16	0.4 6 3	5.0	0 0	0._4	−0.3

[1]) I red cted BF/BCM i 0 36±0 00 (S.D) and fo the female subject No 8 0 54

[2]) Technical failure of leterminati

Table 10 *Effect of physical training and better nutrition on total body water in school children with cerebral palsy I itial values and changes in kg and in TBW/BCM during 9 months of therapy in 13 subjects Additional study one year later*

Index number	Initial observation Predicted lbs Sept 1967	Change during study	TBW[1]) / BCM at start Sept 1967	TBW[1]) / BCM at end June 1968	Additional study Change	TBW / BCM at end June 1969
1	23.4 21.3	−1.0	1.84	1.65	11.8	1.94
	23.3 20.3	−5.3	1.61	1.43	0.6	1.47
4	28.0 22.4	−4.8	1.57	1.28	1.5	1.22
7	17.7 16.1	−0.3	1.72	1.70	2.3	1.90
8	34.5 30.9	−6.4	1.92	1.[illegible]		
11	22. 21.5	−0.1	1.73	1.57	3.9	1.52
14	23.1[2]) 21.1	−1.3	1.80	1.46	3.1	1.74
15	[3])			1.51		
16	24.1 24.0	1.6	1.44	1.49	4.1	1.52
18	20.8 22.5	−2.8	1.66	1.44	3.5	1.65
19	20.7 17.7	2.1	1.91	1.67		
20	18.1[2]) 15.2	1.2	1.66	1.77	0.7	1.75
21	14.4 18.0	−1.3	1.88	1.70	.7	1.66

1) Predicted TBW/BCM is 1.22 ± 0.01 (S.D.) and for subjects Nos. 8 and 16: 1.40.

2) Determination made one month after start of therapy.

3) Technical failure of determination.

TABLE 11 *Effect of physical training and better nutrition on extracellular water in school children with cerebral palsy Initial values and changes in kg and in ECW/BCM during 9 months of therapy in 13 subjects Additional studies were done one year later*

Index number	Initial observation Predicted value Sept 1967	Change during study	ECW[1]) / BCM at start Sept 1967	ECW[1]) / BCM at end June 1968	*Additional* study Change	ECW / BCM at end Jun 1969
1	13 5 8 7	– 4	1 06	0 77	9 4	1 16
2	17 2 1_4	–4 5	0 84	0 65	0 7	0 69
4	19 1 13 3	–6.1	0 79	0 50	1.3	0.64
7	9 7 6.3	–0 3	0 94	0 9	0 7	0.5
8	20 4 13 6	–6.8	1 13	0 74		
11	13 0 8.7	–1 1	0.95	0 79	1.5	0.74
14	11.6[2]) 8.5	–1 6	0.81	0 68	6 4	0 96
15	)			0.73		
16	15.6 13 9	1.5	0 66	0 7	_3	0 74
18	16.3 10.3	–3.5	0 88	0 66	3 8	0 87
19	1 3 7	–_5	1 14	0 88		
20	9 6[2]) 6 4	1 2	0 88	0.99	0 3	0 97
21	8.3 6 7	–1	1 06	0 9	1.3	0.88

[1]) Predicted ECW/BCM is 0 54 ± 0 01 (S D) and f r subject Nos. 8 and 18 0 62

[2]) Determination made ne month fter start of therapy

) Technical failure of determ nation

TABLE 1. *Effect of physical training and better nutrition on body fat in school children with cerebral palsy. Initial values and changes in Iq and in BF/BCM during 9 months of therapy in 13 subjects. Additional studies were done one year later*

Index number	Initial observation Predicted also Sept. 1967	Change during study	BF[1]) / BCM at start Sept. 1967	BF[1]) / BCM at end June 1968	Additional study Change	BF / BCM at end June 1969
1	12.4 5 8	4 1	1 06	1.21	−10 1	0 40
2	16.4 6 6	−1 1	0.79	0 78	−0 7	0 75
4	18.2 8.9	5.0	0 76	0 99	−2.9	0.61
7	4 2 4.0	0.9	0 41	0 50	−0.8	0.34
8	4 5 12.6	6.2	0.25	0.58		
11	10.7 5.7	3 7	0 78	0 47	1.5	0 47
14	9 3[2]) 6.0	−1 9	0 64	0.49	−3 6	0.22
15	[3])			0.41		
16	6.1 7 1	1.0	[illegible]	0 26	−6.1	0.0
18	10.4 10 0	0.1	0.86	0.84	−2.3	0 44
19	3 6 4 8	2 8	0 19	0 40		
20	7 9[2]) 4.1	−0.8	0.72	0.65	0 1	0 63
21	2.6 4 0	1.8	0.76	0 49	−1.8	0.23

[1]) Predicted BF/BCM is 0.34 ± 0.03 (S.D.) and for subjects Nos. 8 and 16: 0.57 and 0.67 respectively

[2]) Determination made one month after start of therapy

[3]) Technical failure of determination.

TABLE 13 *Effect of better nutrition on exchange able body potassium in school children with cerebral palsy Initial values and changes during 9 months of better diet in 8 subjects O=Observed P=Predicted*

I d x \	Initial K (mmol) Sept 1968) O / P	O 100 / P	O 100 / P after diet June 1969[a])
6	915 / 1388	06	00
l	1197 / 1640	73	63
23	11*9 / 1*00	90	86
4	1 11 / 1460	83	113
_5	88 / 1140	77	83
*6	89 / 1100	90	93
7	1 19 / 14*0	86	90
*8	935 / 1030	91	87

[1]) Nos. 6 17 Sept 196
[a]) Nos. 6 17 June 1968

TABLE 14 *Effect of better nutrition on total body water in school children with cerebral palsy Initial values and changes in kg and in TBW/BCM during 9 months of better diet*

Ind x \	Initial observation Predicted value Sept 1968[a])	Change during study	TBW[1]) / BCM t start Sept 1968[a])	TBW[1]) / BCM at end June 1969[a])
6	15.3 / 15 4	−0.3	1 99	1.9
17	*0.4 / 18 0	−_.5	_.04	1.83
*3	16.5 / 14._	)	1 76	)
4	*0.1 / 16 4	3.1	1 99	1.53
_3	13 7 / 1_.7	_	1 85	1.94
*6	15 / 1 4	_5	1 93	1 85
*7	19 0 / 15 8	−0	40	1 61
*8	14 8 / 11.5	)	_1	)

) Predicted TBW/BCM is 1 34±0 04 (S.D)
) Nos. 6 17 Sept. 1967
) Nos. 6, 17 June 1968.
) Technical f ilure f determination

Study C The effects of improved nutrition as the only therapy are given in Tables 13–16 K still was not affected For 5 of 6 subjects with complete data TBW and ECW showed a reduction when related to BCM which is non significant with the sign test BF was increased in 2 of 3 obese subjects and was further reduced in 2 slender subjects

Table 17 gives a summary of the trends found *significant* with the sign test and which have been reported above The means and the standard errors of the differences are also given As seen from the table the total decrease in TBW and ECW in Studies A and B combined amounted to 350 g per kg BCM while the increase in BF during the same period was 180 g per kg BCM

Discussion

In the present longitudinal studies BCM is expressed as per cent of the predicted value Thus changes in this figure express changes other than those caused by growth Consequently TBW and ECW are expressed in kg per kg BCM in order to compensate for growth changes

ECW is calculated on the basis of two and BF on three different determinations (3) Many methodological errors will thus affect the calculations of these two compartments Calculated individual data of changes in ECW and BF must thus be interpreted with precaution Moreover FFECS also influences the estimation of BF However possible relative changes in FFECS during the longitudinal studies are regarded as negligible

TABLE 15 *Effect of better nutrition on extra cellular water in school children with cerebral palsy Initial values and changes in kg and in ECW/BCM during 9 months of better diet.*

Index No	Initial observation Predicted value Sept. 1968[2])	Change during study	ECW[1]) / BCM at start Sept. 1968[2])	ECW[1]) / BCM at end June 1969[3])
6	9.3 8.4	−0.4	1.21	1.14
17	12.6 7.4	−2.4	1.26	1.04
23	9.1 8.0	[4])	0.97	[4])
24	12.2 8.9	−0.4	1.31	0.80
25	7.9 6.3	1.6	1.07	1.16
26	9.2 8.2	1.1	1.19	1.10
27	11.1 6.6	−1.4	1.09	0.83
28	8.7 4.8	)	1.13	)

[1]) Predicted ECW/BCM = 0.90±0.01 (S.D.).
[2]) Nos 6, 17 Sept. 1967
[3]) Nos 6, 17 June 1968.
[4]) Technical failure of determination.

TABLE 16 *Effect of better nutrition on body fat in school children with cerebral palsy Initial values and changes in kg and in ECW/BCM during 9 months of better diet*

Index No.	Initial observation Predicted value Sept 1968[2])	Change during study	BF[1]) / BCM at start Sept. 1968[2])	BF[1]) / BCM at end June 1969[3])
6	4.1 4.1	+0.4	0.53	0.56
17	19.6 6.0	+3.3	1.96	.40
23	1.4 3.7	[4])	0.15	[4])
4	2.2 4.2	0.6	0.22	0.20
25	4.1 3.3	−2.6	0.54	0.18
26	2.6 3.2	−1.5	0.33	0.11
27	1.6 4.0	2.3	0.16	0.38
28	1.1 2.9	[4])	0.14	)

[1]) Predicted BF/BCM = 0.35±0.03 (S.D.)
[2]) Nos. 6, 17 Sept. 1967
[3]) Nos. 6, 17 June 1968.
[4]) Technical failure of determination.

The physical training increased the physical capacity of the subjects (1) The dietary recordings reveal that the improved diet was accepted and increased the intake of essential nutrients within the limits set by the still relatively low energy need. Several subjects however showed an insufficient nutrition in one or several respects. It is difficult to evaluate the significance of the low intake of iron in several subjects as the hemoglobin determinations are uncertain, see discussion in a previous paper (3). The calcium intake was often below the recommended amount without a significant influence on the growth rate of the subjects

The three longitudinal studies were intended to give some indication of the relative importance of physical activation and of nutrition. In Study A, the introduction of physical training was the only change of routine The dietary intake was not recorded. However all subjects accumulated fat, which clearly indicates that the food intake also was affected The BF increase corresponds to a mean daily overconsumption of 200 kcal This positive energy balance in combination with an increased physical activity should allow a better supply of essential nutrients than before In Study C the plan was to change the diet alone. However all subjects were new at the Centre, and this may have increased their activity In a previous study (1) it was found that summer vacation significantly reduced the physical working capacity indicating a lower physical activity at home. The Centre can offer bigger areas for ambulation than the homes can. Thus the dietary treatment in Study C was probably combined with

Table 17 *Summary of the effects of therapy in Studies A, B and C as found with the sign test. For trends found significant the level of significance is given as well as the means and the standard errors of the differences. The difference is calculated as final value less initial value and is given in kg per kg BCM*

Study	K	TBW	ECW	BF
A	0	$p<0.01$ −0.26±0.03	$p<0.01$ −0.[illegible]6±0.05	$p<0.01$ +0.[illegible]3±0.03
B	0	$p<0.05$ −0.16±0.04	$p<0.05$ −0.16±0.04	0
A+B	0	$p<0.01$ −0.35±0.05	$p<0.01$ −0.35±0.05	$p<0.05$ 0.16±0.07
C	0	0	0	0

activation, though hard to grade. Nevertheless, in Study A the main therapeutic approach was the increased activity, in Study C the improved nutrition.

As stated in the introduction, malnutrition and inactivity were considered relevant causes of the abnormalities of the body composition *in this material*. The effects on ECW found in the longitudinal studies support these assumptions.

During the longitudinal studies the growth of the subjects proceeded as before. The absence of a growth spurt after the improved diet had been introduced (Study B) indicates that the subjects had not been severely malnourished before the start of the studies.

The *training imposed on the subjects* could be expected to increase the muscle mass (and thus K). The training affected the observed maximal oxygen uptake of these subjects (1) without significant changes in K. This must indicate that the training improved the muscular capacity by a better circulatory and metabolic adaptation.

As for the changes in BF, it should be noted that the directions of the changes in Studies A and B are uniform and the trend significant. In the obese subjects the trend was not the expected one. It was hoped that the increased physical activity should improve the energy balance (7, 8). In previous studies physical activation as only therapy has also been reported to reduce the fat mass of obese children (5). However, physical activation with the expected results has often been combined with a restriction of the energy intake (9). Physical training as the only therapy has also been reported by Björntorp *et al.* (4). Their obese subjects, however, increased their fat mass during physical training, as did ours. It should be noted that the combination of physical training and a more nutritious diet (Study B) resulted in a decreased BF in 3 obese subjects.

The observed reduction in BF during the study after Study B was in conformity with the observed voluntary reduction in energy intake. This in turn may have been caused by some food dislike due to the relatively rigid menu (a 5-week cycle) difficult to avoid in an institution.

In analysing the above therapeutic effects, it must be kept in mind that several other environmental factors and the subject's personality must influence the way in which the child responds to therapy, and that such variables are hard to fully evaluate. Nevertheless, it can be concluded that the body composition in all subjects, with a few exceptions, was better at the end of the studies than before, and that none was worse.

Studies of the spontaneous growth pattern in very small children and of the effect of early treatment will probably give more indications as to the nature of growth retardation and changes in body composition in cerebral palsy

Summary

Twenty two subjects with cerebral palsy and with abnormal body composition, reduced physical activity and malnutrition, were subjected to treatment with physical activation and/or improved nutrition. Nine subjects were trained for 4 months (Study A). 8 of these and 5 more subjects then received training and improved nutrition during one school-year (Study B). Eight more subjects had only the improved nutrition for one school year (Study C).

The treatment in Studies A, B and C had no significant effect on the initially reduced body cell mass (BCM).

The markedly increased extracellular water (ECW) was significantly reduced in Studies A and B but not in C.

The effect of the treatment on body fat (BF) varied. In Study A the body fat increased significantly, in Studies B and C no significant changes were observed.

The effects were interpreted as evidence of the fact that inactivity and malnutrition were relevant causes of the abnormal body composition. The observed absence of a growth spurt during the therapy indicated that the initial malnutrition could not have been too serious. A clear-cut separation between the two therapeutic measures was not achieved however as an increased activity induced an increased intake of energy and of essential nutrients.

Acknowledgements

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B	0	$p<0.05$ -0.16 ± 0.04	$p<0.05$ -0.16 ± 0.04	0
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Energy requirements of school children with cerebral palsy as determined from indirect calorimetry

by KRISTINA BERG and TORSTEN OLSSON

The assessment of energy expenditure in subjects with cerebral palsy is of profound importance in recommending the optimal nutrition. Due to the handicap of the subjects, their physical activity is restricted to a degree determined by the severity and type of the disability. This means that their energy consumption is affected. In a previous study it was shown that the intake of energy was low (6). Since the need for essential nutrients is not dependent on the total energy turnover (7), diets for subjects with a low energy need must be carefully planned so as to contain enough essential nutrients per unit of energy.

The heart rate can be used as an indirect measure of oxygen uptake and energy needs, for instance when testing the physical working capacity (1). At moderate and high work loads, the oxygen requirements of the work alone set the levels of the circulatory parameters including the heart rate. At low levels of physical activity other factors than the oxygen need are said to influence the heart rate. Such factors include excitement and tension. Variations in the heart rate in one individual during habitual conditions have nevertheless been used as a relative measure of variations in energy demands (2, 3).

Since the heart rate can be recorded continuously with telemetric equipment with little or no discomfort to the subject, such recordings were made on a group of children with cerebral palsy to establish the pattern of the heart rate variations in severely handicapped subjects during different activities. Intermittent collections of expired air for gas analysis were performed in order to study if there was a relationship between oxygen uptake and heart rate at low activity levels. If so, these two types of determinations in one subject could form the basis for the evaluation of the 24 hour energy demand. The results obtained in this way will be reported in the present paper.

Material

The main study (A) with repeated gas analyses and long term registration of the heart rate was carried out on four full board subjects, Nos. 17, 18, 25 and 27. Six other full board subjects were investigated in a less comprehensive study (B). Details of the subjects are given in Table 1.

Methods and procedure

Body size determination. Body height (BH) and body weight (BW) were determined under standardized conditions. Body cell mass (BCM) and body fat (BF) were calculated on the basis of exchangeable body potassium and total body water as determined with isotope dilution methods reported elsewhere (6).

Heart rate monitoring was carried out by means of an FM-telemetric device. The ECG signal was picked up by two floating Ag/AgCl electrodes. After amplification the signal was modulating a 223 MHz transmitter without any subcarrier. A standard FM tuner was used as a

TABLE 1 *Study of energy expenditure in school children with cerebral palsy*
Somatic characteristics of the 10 subjects

Subject No	Sex m = male f = female	Age years	Body height m	Body weight kg	Body cell mass kg	Cerebral palsy tonus	Way of ambulation
17	m	14	146	64 0	1[illegible]4	spastic	wheel hair
18	f	10	150	51 5	19 1	dyskinetic	self ambulant
[illegible]3	m	8	110	[illegible]2.0	8	spastic	wheel hair
[illegible]7	m	8	131	[illegible]0 0	11	dyskineti	self ambulant
4	n	[illegible]3	166	1 0	6	pastic	self ambulant
15	m	10	108	5[illegible]5	1.5	spastic	wheel hair
10	m	10	160	53 5	23 9	dyskinetic	wheel hai
19	m	13	141	[illegible]9 0	11	dyskinetic	self ambulant
[illegible]0	m	1	130	3[illegible]5	10 9	spastic	wheel hair
1	f	10	131	1 0	7 7	dyski etic	self ambulant

receiver and was modified with a premixer to convert the 223 MHz to about 100 MHz. The AFC-signal was used as output after decreasing the time constant to get sufficient band width The demodulated signal was then amplified and filtered in an optimal pulse filter to minimize disturbance from the EMG signals The QRS wave triggered the heart rate meters. A beat per beat tachometer showed the heart rate directly on a meter An integrating rate meter with a time constant of 5 seconds was used to feed a Minuscript recorder with a paper speed of 2 mm per minute and a writing speed of one point every 2 seconds to get continuous recordings The accuracy of the rate meter was checked by recording the ECG signal on an Elema-Schönander Mingograph where the heart rate was calculated manually The maximal error of the beat per beat tachometer was 3 per cent and the corresponding value in a steady state for the integrating tachometer was 2 per cent The best positions of the electrodes proved to be on the forehead for the indifferent electrode and on the sternum at ribs 4 and 5 for the detector electrode

Collection of expired air was done in Douglas bags during 5-minute periods The rubber mouth piece was combined with the special rubber membrane described previously (5) Gas analysis was performed according to Scholander (10) All subjects except No 27 were thoroughly familiar with air collection procedures With No 27 there were no particular problems.

Heart rate monitoring was performed in periods of about three hours In the intensively studied group various daily activities were covered in the recordings e.g different types of school lessons spare time activities, meal dressing undressing and washing and going to sleep (Figs 1 and 2) Sampling of air was also performed during common activities In the less thoroughly studied group monitoring periods and air collections were selected on the basis of the same principles but the number of determinations was smaller

Calculation in Study 4 of the 24 hour energy expenditure on the basis of these determinations was performed as follows The mean heart rate was determined for each recorded period of five minutes and then plotted on a 24-hour diagram for each subject This permitted a survey of the heart rate pattern of that individual Then the various activities during one day were grouped according to muscular effort For instance being in bed probably requires the same energy throughout the period The daily life at school is a sedentary activity most of the time Being at home (in the institution) can involve a great variety of efforts, such as eating playing and dressing but these efforts are



Fig. 1 Telemetric device for heart rate monitoring. Subject 27

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On the basis of th mean heart rat during an acti ity the xygen uptake corresponding to that heart rat could be estimated from the individual regression line The 24-hour oxygen uptake is the sum of the various activities during one day The oxygen uptake was transformed to energy by assuming a calorific equi valent of 4.8 kcal per liter oxygen consumed and a respiratory quotient of 0 82

The calculation of the 4-hour energy expendi ture in Study B was based on the methods and results obtained in Study A. A regression analysis of the pooled figures of the oxygen uptake per kg BCM at various heart rates of all A and B subjects was performed The oxygen uptake at heart rate 5 as intrapolated on the regression line was used as "basal point of oxygen uptake (see Results and Discussion) The indi vidually determined oxygen uptake at a known heart rate or the average of two such deter minations, was connected with the basal" point This line replaced the regression lines of the

TABLE 1 *Study of energy expenditure in school children with cerebral palsy*
Somatic characteristics of the 10 subjects

Subject No	Sex m = male f = female	Age years	Body height cm	Body weight kg	Body cell mass kg	Cerebral palsy tonus	Way of ambulation
17	m	14	146	64 0	12.4	spastic	wheel chair
18	f	19	150	51.5	19 1	dyskinetic	self ambulant
5	m	8	119	–.0	8	spastic	wheel chair
*7	m	8	131	29 0	11 7	dyskinetic	self ambulant
4	m	23	166	71 0	*6.–	spastic	self ambulant
15	m	19	168	52.5	21 5	spastic	wheel chai
16	m	19	166	53 5	23 9	dyskinetic	wheel chair
19	m	13	141	*9 0	11.–	dyskinetic	self ambulant
*0	m	1	130	3 5	10 9	spastic	wheel chai
1	f	10	131	1 0	7 7	dyskinet	self ambulant

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Collection of expired air was done in Douglas bags during 5-minute periods The rubber mouth piece was combined with the special rubber membrane described previously (5) Gas analysis was performed according to Scholander (16) All subjects except No 27 were thoroughly familiar with air collection procedures With No 27 there were no particular problems.

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Calculation in Study A of the 24 hour energy expenditure on the basis of these determinations was performed as follows The mean heart rate was determined for each recorded period of five minutes and then plotted on a 24 hour diagram for each subject This permitted a survey of the heart rate pattern of that individual. Then the various activities during one day were grouped according to muscular effort For instance being in bed probably requires the same energy throughout the period The daily life at school is a sedentary activity most of the time Being at home (in the institution) can involve a great variety of efforts, such as eating playing and dressing but these efforts are



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probably performed in a fairly constant manner by each individual and can be grouped as home activities The mean heart rate for each group of activity could then be determined on the basis of the recordings The time spent on different activities was also thoroughly investigated for each subject

Another step was regression analysis of all sets of oxygen uptake and the mean heart rate at which it was measured for each individual. From this line the oxygen uptake at any heart rate within the recorded limits was read.

On the basis of the mean heart rate during an activity the oxygen uptake corresponding to that heart rate could be estimated from the individual regression line The 24-hour oxygen uptake is the sum of the various activities during one day The oxygen uptake was transformed to energy by assuming a calorific equivalent of 4.8 kcal per liter oxygen consumed and a respiratory quotient of 0.82

The calculation of the 24-hour energy expenditure in Study B was based on the methods and results obtained in Study A. A regression analysis of the pooled figures of the oxygen uptake per kg BCM at various heart rates of all A and B subjects was performed. The oxygen uptake at heart rate 75 was intrapolated on the regression line was used as "basal" point of oxygen uptake (see Results and Discussion) The individually determined oxygen uptake at a known heart rate or the average of two such determinations, was connected with the basal point. This line replaced the regression lines of the



Fig — T lemetric levice f r heart rat mon toring Subject *7

subjects in Study A and was used in the same way The heart rates for Study B subjects at home or in bed were found empirically from experience with Study A and from observations of the subject s behaviour at home if he was more less or similarly active as at school The values of the heart rate when the subject was in bed were given the value 88 for the youngest subjects and 83 and 78 in the older

To *compare* the energy demands in individuals of different sizes calculations were done per kg BW and BCM

Dietary recordings and calculations were per formed as described previously (6) The value given is the mean 24-hour energy intake during 4–5 days

Results

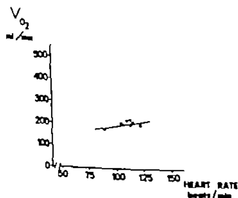
The heart rate patterns of two children are seen in Fig 3 Each point is the mean value of a 5-minute registration Subject 17 was obese and unable to walk His heart rate pattern was remarkably uniform for long periods of time even though his activities changed during the recorded periods In agreement with his heart rate pattern, the relation between minimal oxy gen uptake and maximal oxygen uptake recorded for him was 1 1.3 Subject 27 was the opposite in behaviour His heart rate pattern showed considerable variations His oxygen uptake gave a ratio of *1.2* 7 between minimal and maximal uptake



I Heart rate during one day If repeated monitoring was done t the same time of the day only results one occasion are given. Also, no essential difference was found between two or more registrations during the same activ ty (Fig 8). Subjects 17 and 27

e oxygen uptake as recorded for these two ects and the corresponding heart rates are in Figs. 4 and 5 The line of correlation dicated

regression analysis was performed on the s of oxygen uptake per kg BW and BCM the corresponding heart rates. The corre- n coefficient was 0 01 for oxygen per kg I and only 0.30 per kg BW For this reason, her calculations were always based on BCM ig 6 shows the regression lines and the correlation coefficients for Study A subjects and the common line for all ten subjects. Each line is significant judged by the r value and there is also a significant difference between the slopes of the four individual lines. Four lines coincide at a heart rate of about 75 and at an oxygen uptak of about 11.5 ml/min × kg BCM. The smallest range of heart rates were found for an oxygen uptake of 13 ml/mm × kg BCM. The 95 per cent confidence interval of heart rate at this oxygen uptako is 0–90 beats per minute



. 4. Oxygen uptake at arious heart rates and line of regression. Subject 17

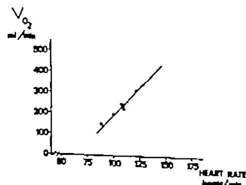


Fig 5. Oxygen uptake at various heart rates and line of regression. Subject 27



Fig   Telemetric device for heart rat monitoring Subject 27

subjects in Study A and was used in the same way The heart rates for Study B subjects at home or in bed were found empirically from experience with Study A and from observations of the subject's behaviour at home if he was more less or similarly active as at school The values of the heart rate when the subject was in bed were given the value 88 for the youngest subjects and 83 and 78 in the older

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TABLE Study of e ergy expenditure in school hildren with cerebral palsy Data used for calculation f energy expend ture

Subject No.	In bed: Time hours	In bed: Heart rate beats/min	In bed: Oxygen uptake ml/min kg DCM	At school: Time hours	At school: Heart rate beats/min	At school: Oxygen uptake ml/min × kg DCM	At home: Time hours	At home: Heart rate beats/min	At home: Oxygen uptake ml/min × kg DCM
17	9	80	14 4	7 5	114	17.3	7.5	106	16.3
18	8	75	9 6	8	98	13 6	8	110	16.2
25	11	85	17 0	4	103	23 2	9	110	26.0
27	11	80	11 6	4	111	21 6	9	116	23 0
4	8	78	11 6	8	90	12.3	8	90	13.3
15	8	83	11.8	8	97	13.0	8	97	13 0
16	8	80	14.5	8	95	17.3	8	105	20 0
19	9	88	16.2	6	100	20 7	9	113	23 7
20	10	84	13 6	6	107	17 4	8	100	16.1
21	10	85	14.0	6	111	18.9	8	120	21 1

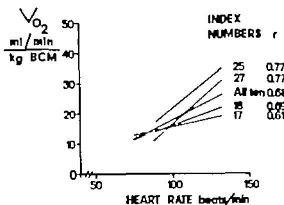


Fig 6 Regression lines of oxygen uptake versus heart rates for Study A subjects and the line for all ten subjects.

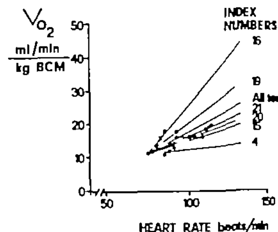


Fig 7 Construction of lines of heart rates at various oxygen uptakes for Study B subjects. Each dot represents one determination. For subject with two determinations, an average of the two values was used as indicated by the dashed lines.

The regression line common for all subjects gives a heart rate of 82 at the oxygen uptake of 13 ml

Fig 7 shows the lines constructed for Study B subjects The mean heart rate and one standard deviation for the four groups of activities are given in Fig 8 where the time monitored also is indicated For all subjects significantly different levels for each activity were found and the various activities in one individual also showed significantly different levels

Table 2 gives data for calculation of total energy expenditure per day as found on the basis of the oxygen uptake lines of Figs 6 and 7 from the heart rates of Fig 8 and from individual registration of the time spent at various activities

Table 3 gives the total energy expenditure calculated as above and on the basis of dietary recordings To evaluate the accuracy the nutritional state of the subject is indicated as BF per kg BCM

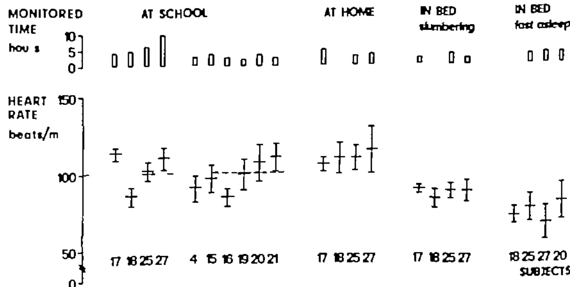


Fig 8 Heart rate during various activities. Mean value, one standard deviation and the time monitored are given for different subjects.

Table 2 *Study of energy expenditure in school children with cerebral palsy. Data used for calculation of energy expenditure.*

Subject N	In bed			At school			At home		
	Time hours	Heart rate beats/min	Oxygen uptake ml/min kg BCM	Time hours	Heart rate beats/min	Oxygen uptake ml/min kg BCM	Time hours	Heart rate beats/min	Oxygen uptake ml/min x kg BCM
17	9	69	14.4	7.5	114	17.3	7.5	106	16.2
13	8	79	9.8	6	96	13.6	8	110	18.2
25	11	88	17.0	4	103	22.3	8	110	26.0
27	11	89	11.6	4	111	21.6	9	115	23.0
4	8	78	11.8	8	90	13.3	8	90	13.3
15	8	83	11.8	8	97	13.0	8	97	13.0
14	8	80	14.5	8	88	17.3	8	105	19.0
19	9	88	16.2	6	100	20.7	9	113	23.7
20	10	88	13.6	6	107	17.4	8	100	16.1
21	10	68	14.0	6	111	18.9	8	120	21.1

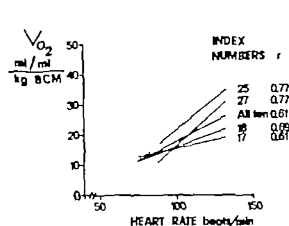


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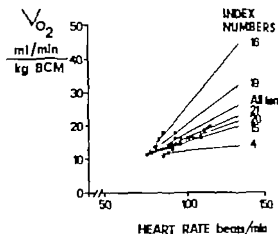


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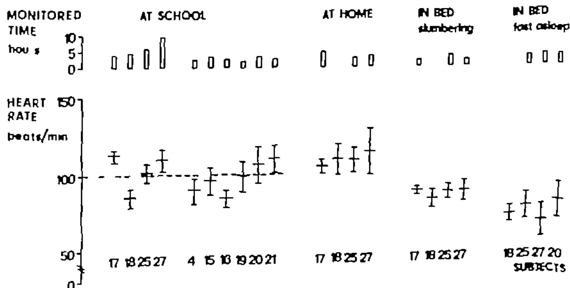


Fig 8. Heart rat d ring various acti ities. Mean value, one stand rd deviation and the time monitored are given for different subjects.

sitting such as in front of a television set or playing game with friends, or at school. If emotional stress increases the heart rate but not the oxygen uptake it would explain the lower correlations found in our subjects, compared with those of Bradfield (8) Compared with the heart rate monitoring the air collection procedure interferes more with the activity performed This, too can affect the calibration Nevertheless, only in one instance of all 60 determinations of oxygen uptake in Study A did the heart rate change markedly during the air collection (more than 5 beats/min) compared with periods before and after The calibration of the relationship between heart rate and oxygen uptake was done with the assumption of a linear relationship between these variables. In their systematic study of the relationship Bradfield *et al.* found th t the deviation from the straight line was very small and they concluded that, for practical purposes, it was not of importance (8).

During the subject s heavy midnight sleep w recorded lower heart rates than in early morning With the present air collection equipment it as not possible to get air collections without the cooperation of the subject Since the early morning determinations, however were performed during conditions that can be considered basal, the values obtained were considered representative for th whole ight The use of the lower heart rate for extrapolation on the regression line was not considered correct here as it is quite possible that the low heart rate during sleep is due t a circulatory redistribution without a concomitant change of oxygen uptake

The cross-over of the regression lines at heart rates of 75–80 and an oxygen uptake of 11 5–13 might be a coincidence since the material is ery small. Nevertheless from a theoret cal point of view t is of considerable interest since there should be a point f absolute basal needs of the cell This point should represent the minimum oxygen requirement for basal metabolic processes in a thermoneutral environment There re no reasons to believe that such a minimum oxygen need per unit cell mass should differ individually if one disregards the possible influence of age. From a different approach such an absolute basal need has been calculated to be 8–10 ml/min × kg BCM (14)

The fanning of lines from this absolute basal point can be explained by a different aerobic capacity of the subjects Individuals with a good circulatory ability transport more oxygen per heart beat, and their lines would show a strong increase Lines with low slopes then represent subjects with a low aerobic capacity The aerobic capacity found for these subjects in other studies (4) generally agree with this statement

The conclusion of this would be that individual calibration of the relationship between oxygen uptake and heart rate is necessary for the use of th heart rate in evaluation of energy expenditure, if the subjects differ greatly in aerobic capacity as in the present study

The accuracy of the energy expenditure as evaluated with our method cannot be calculated directly as the absolute value cannot be determined The best indication of the accuracy would probably be found if the data were correlated with the data of the subjects nutritional state as done in Table 3 The generally good fit is obvious, i e. subjects with an evaluated high energy expenditure and a recorded lower energy intake show small fat deposits and vice versa. Nor is there any obvious discrepancy between the results of Study A and B Two exceptions from the good agreement are found, however i.e. subjects Nos 17 and 21 The former was known to consume great quantities of sweets secretly so his dietary recordings may be representative of food intake but not of his habitual energy intake which could be 1000 kcal higher or more For Subject 21 the dietary recordings agree well with her eating patterns. Thus her activity must be under estimated with our method The procedure in Study A thus seems to give a good estimate of energy expenditure. It is of interest that even one or two determinations of oxygen uptake and calculations with a predetermined "basal

Discussion

Evaluation of energy expenditure in subjects with cerebral palsy has been performed previously first probably by Phelps in 1050 (15) He based his conclusions on energy intake calculated for individual dietary recordings This indirect method has been used later by other investigators (11 12) Although the method probably gives a good approximation of energy expenditure in healthy populations its application to subjects with cerebral palsy is open to criticism as feeding difficulties are common in such subjects and can modify the intake

Direct and continuous determinations of oxygen uptake have also been attempted with the Wolff Integrating Motor Pneumotachograph (17) This apparatus is said to be very convenient and has been used continuously for days on men in military service for instance (10) Eddy *et al* concluded however that this method was not well suited for subjects with cerebral palsy as they were bothered by the facial mask and could tolerate it only for periods of less than one hour (9)

Direct determinations of specified activities such as walking have also been performed on subjects with cerebral palsy and indicate a higher energy demand for such activities than in healthy subjects (13)

Prediction of energy requirements on the basis of heart rate registration is a common approach since heart rate recording is simple The calibration of the relationship between heart rate and oxygen uptake has been done in various ways. In Swedish studies oxygen uptake during bicycle ergometer tests have been used (2 3) Such an approach is not applicable to very inactive subjects as their habitual heart rates are below those found in the tests

This difficulty was observed by Bradfield *et al* (8) who calibrated by measuring the oxygen uptake at six different basal activities such as lying sitting and standing Regression analysis of oxygen uptake and heart rate gave a good linear correlation

In our studies, we used a telemetered heart rate for continuous registration as we were also interested in occurrence of variation. We do not consider that our equipment is inconvenient for the subjects They were studied in their natural environment and continued all their daily activities during the study

To calibrate the relationship between oxygen uptake and heart rate we used an approach similar to Bradfield's In addition to this we tried to catch the emotional overtones affecting the correlation, by direct determination of oxygen uptake during for instance various types of

TABLE 3 *Daily energy expenditure of school children with cerebral palsy as found in the present study and their nutritional state as indicated by dietary intake of energy and body fat (BF) in kg per kg body cell mass (BCM) at the study and 8 months before the study*

Subject No	Present study kcal	Dietary intake kcal	BF¹) / BCM at study	BF¹) / BCM before study
1	1350	950	0.24	0.34
18	1650	1750	0.44	0.5
25	[illegible]	1400	0 18	0 66
27	1400	1650	0 35	0 16
4	2300	[illegible]	0 89	0.59
15	1900	[illegible]	0 41	0 11
16	3350	3150	[illegible]	0 0
19	1600	[illegible]	0 40	0 15
20	1150	1350	0 65	0 66
21	950	1600	0 49	[illegible]

sitting such as in front of a television set, or playing a game with friends, or at school. If emotional stress increases the heart rate but not the oxygen uptake it would explain the lower correlations found in our subjects, compared with those of Bradfield (8) Compared with the heart rate monitoring, the air collection procedure interferes more with the activity performed. This too can affect the calibration. Nevertheless, only in one instance of all 50 determinations of oxygen uptake in Study A did the heart rate change markedly during the air collection (more than 5 beats/min) compared with periods before and after The calibration of the relationship between heart rate and oxygen uptake was done with the assumption of a linear relationship between these variables. In their systematic study of the relationship Bradfield *et al* found that the deviation from the straight line was very small and they concluded that, for practical purposes, it was not of importance (8)

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The conclusion of this would be that individual calibration of the relationship between oxygen uptake and heart rate is necessary for the use of the heart rate in evaluation of energy expenditure if the subjects differ greatly in aerobic capacity as in the present study

The accuracy of the energy expenditure as evaluated with our method cannot be calculated directly as the absolute value cannot be determined The best indication of the accuracy would probably be found if the data were correlated with the data of the subjects nutritional state as done in Table 3 The generally good fit is obvious, i.e subjects with an evaluated high energy expenditure and a recorded lower energy intake show small fat deposits and vice versa. Nor is there any obvious discrepancy between the results of Study A and B Two exceptions from the good agreement are found however i.e. subjects Nos. 17 and 21 The former was known to consume great quantities of sweets secretly so his dietary recordings may be representative of food intake but not of his habitual energy intake which could be 1000 kcal higher or more For Subject 21 the dietary recordings agree well with her eating patterns. Thus her activity must be underestimated with our method. The procedure in Study A thus seems to give a good estimate of energy expenditure It is of interest that even one or two determinations of oxygen uptake and calculations with a predetermined basal

point as in Study B seem to give an equally good estimate

Acknowledgements

This study was supported by grants from the Medical Faculty University of Göteborg and from Första Majblommans Riksförbund

Summary

Four subjects with severe cerebral palsy were studied with heart rate telemetry and intermittent sampling of expired air for gas analysis while they performed their habitual activities

For each subject a significant relation between oxygen uptake and heart rate was found On the basis of the heart rate recordings and the time spent on various daily activities, a mean heart rate was found for each subject The corresponding mean daily oxygen uptake was read from this line

The four individual lines of the correlation between oxygen uptake and heart rate differed significantly from each other with respect to the slope. Three of 4 lines crossed over at a heart rate of about 75 beats per minute and oxygen uptake of 11.5 ml per minute and kg body cell mass This was regarded as a "basal point representing the basal cellular need in a thermoneutral environment

This basal point was used for calculation of energy expenditure in a less extensive study of 6 subjects In these children only one or two air analyses at a known heart rate were performed This determination or the average of two determinations was connected with the basal" point The individual line was then used to determine the mean daily oxygen uptake

The mean daily energy expenditure found for the ten subjects agreed well with the energy intake from dietary recordings on the one hand and body fat amounts on the other

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Somatic adaptation in cerebral palsy—summary and general discussion

by KRISTINA BERG

In this part a summary will be made of the studies of indirect sequelae in cerebral palsy at school age. The material studied, the methods employed and their relevance, and the main results will be surveyed. A general discussion will then integrate the results of the different studies.

The following parts will be discussed.

I. School children with cerebral palsy at Bräcke Östergård Pediatric Habilitation Centre. Cerebral palsy—definitions and incidence. Habilitation—organization and methods. The subjects of the studies—their management and representativity (19)

II. Methods for evaluation of the physical working capacity of school children with cerebral palsy (5)

III. Effect of physical training of school children with cerebral palsy (3)

IV. Dynamic and static lung volumes of school children with cerebral palsy (9)

V. Body composition and nutrition of school children with cerebral palsy (6)

VI. Effect of physical activation and of improved nutrition on the body composition of school children with cerebral palsy (4).

VII. Energy expenditure of school children with cerebral palsy as determined from indirect calorimetry (8)

The parts will be cited with their Roman numeral in the text.

The following abbreviations will be used

BCM – body cell mass (calculated from K)
BH – body height
BW – body weight
ECW – extracellular water (TBW–ICW)
FFECS – fat-free extracellular solids (12% of BW)
ICW – intracellular water (70% of BCM)
K – total exchangeable body potassium (determined with ^{42}K)
TBW – total body water (determined with tritium)

point as in Study B seem to give an equally good estimate

Acknowledgements

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Summary

Four subjects with severe cerebral palsy were studied with heart rate telemetry and intermittent sampling of expired air for gas analysis while they performed their habitual activities

For each subject a significant relation between oxygen uptake and heart rate was found On the basis of the heart rate recordings and the time spent on various daily activities, a mean heart rate was found for each subject The corresponding mean daily oxygen uptake was read from this line

The four individual lines of the correlation between oxygen uptake and heart rate differed significantly from each other with respect to the slope Three of 4 lines crossed over at a heart rate of about 75 beats per minute and oxygen uptake of 11.5 ml per minute and kg body cell mass. This was regarded as a "basal" point representing the basal cellular need in a thermoneutral environment

This "basal" point was used for calculation of energy expenditure in a less extensive study of 6 subjects In these children, only one or two air analyses at a known heart rate were performed This determination, or the average of two determinations was connected with the "basal" point The individual line was then used to determine the mean daily oxygen uptake

The mean daily energy expenditure found for the ten subjects agreed well with the energy intake from dietary recordings on the one hand and body fat amounts on the other

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rate of about 78 beats per minute and an oxygen uptake of 11.5 ml per minute per kg BCM. This cross-over point was used when studying six other subjects. For each of these subjects, single or double determinations of oxygen uptake at a known heart rate were connected with a straight line to the point where the regression lines coincided. These lines, combined with heart rate recordings during different activities, were used as the regression lines in the first study to determine the mean daily oxygen uptake.

Therapeutic methods (Parts III and VI). For physical training the subjects had three 20 minute periods a week with activities involving large muscle groups and giving high heart rates during training. For this purpose special methods had to be developed for several subjects.

To study the effect of improved nutrition, a new menu was designed, which had a higher content of essential nutrients per unit energy. Dietary recordings revealed that the new diet was accepted and the nutrition improved.

Discussion of methods

The methods used in the studies of somatic adaptation in the subjects with cerebral palsy represent different degrees of modifications of methods used in clinical routine or in experimental work. This discussion will be concerned with the need of such an adaptation of the methods. The modified technique will also be evaluated.

Lung volumes were determined with conventional clinical methods. The possible obstacles were recognized to be difficulties of adequate instruction and of cooperation. Special precaution was taken in advance to avoid these difficulties.

In longitudinal studies of *body composition* during growth and during physical training anthropometric measurements and body densitometry are the methods commonly used (18, 1). In studies of BF changes during physical training the skinfold measurements alone may be sufficient, as there exist well documented studies of the relation of such determinations and the total fat mass in a subject (10, 23). However these methods do not admit separate estimates of ECW and BF. As both these departments were disturbed in the subjects with cerebral palsy (Part V) isotope dilution methods for direct determinations of the different compartments had to be used in these studies.

A late development of the *isotope dilution techniques* is peroral ingestion of isotopes and determination of the specific activity in urine samples. Such an approach was considered a prerequisite for longitudinal body composition studies in children and excluded the use of other isotopes, for which blood samples are required. According to the accumulated experience of the Metabolic Laboratory there is no need for direct determination of the extracellular compartment as ECW calculated from TBW—ICW (used in the present studies) agrees well with ECW determined from radiosodium (17).

As discussed in Part VI, the calculations of the different body compartments based on three direct determinations (BW, TBW, K) involve several assumptions. This means that the absolut figures indicating a change must be interpreted with caution in individual subjects.

It was not possible to determine the *aerobic power* as limited by circulatory factors, since muscular factors often limited the physical performance of the subjects before their circulatory capacity was exhausted, as judged by an observed low maximal heart rate without lactic acid accumulation. The *graphical method* developed for these subjects made it possible to estimate changes in oxygen uptake at submaximal levels. In addition, the effect of training on the muscular efficiency could be determined on the basis of the increase in the observed maximal heart rate. The final result of training could be evaluated on the basis of these two aspects.

Determinations of the *spontaneous physical activity* were performed according to principles already applied. The identification of a coinciding point for the regression lines is of considerable theoretical interest. The use of this

Material

As cerebral palsy is a multidimensional and dynamic problem involving a wide variety of individual disturbances in addition to the uniting sign of motor disability the access to a well-defined and representative material is essential This was found at Bräcke Östergård Pediatric Habilitation Centre The general policy of the institution and its organization is presented in Part I A close collaboration between those responsible for the care of children with cerebral palsy has been established in western Sweden All affected children are evaluated in a uniform way in determining their need for full board care at Bräcke Östergård The incidence of cerebral palsy in the region was 1 75 pro mille in 1958–1967 Seventeen per cent of all affected children born 1946–1961 became full board students at Bräcke Östergård Approximately half of these get their entire elementary school education at Bräcke Östergård These students are considered representative of the children with severe cerebral palsy in the region The 41 subjects investigated were selected from this group The selection was guided by the requirements of the different studies. In this way subjects with a predominant motor handicap and minor associated handicaps were selected They represented two main groups of cerebral palsy spasticity (22 subjects) and dyskinesia (19 subjects)

Methods

Tests of physical working capacity (Part II) As the mechanical efficiency was found to vary inter and intra individually the indirect methods based on determination of heart rate at a known load could not be used Furthermore many children with severe handicaps cannot participate in collection of expired air at maximal work intensities. Often muscular not circulatory limitations to hard work were found For these reasons a graphical method was worked out It was based on determinations of oxygen uptake at submaximal heart rates and permitted comparisons between different oxygen uptake capacities at submaximal levels By extrapolation to a separately determined maximal heart rate a rough estimate of the observed maximal working capacity could be made This observed capacity could often be limited by muscular inefficiency and thus is not equivalent to the aerobic power where the limits are circulatory

Lung volumes (Part IV) The Bernstein spirometer was used to determine the vital capacity and the forced expired volume in one second Total lung capacity was determined with the Helium dilution method Peak flows were measured with Wright's peak flow meter The technical assistant was well acquainted with all subjects

Body composition (Part V) Total body water (TBW) was determined by an isotope dilution method using tritiated water as tracer The body cell mass (BCM) was estimated on the basis of the total exchangeable body potassium (K) with ^{42}K as tracer The isotopes were given perorally and the specific activity measured in duplicate urine samples collected after the equilibration period Extracellular water (ECW) and body fat (BF) were calculated on the basis of these two determinations and on body weight (BW) The predicted body composition was based on body height (BH) and age of the subjects

Nutrition (Part V) Intake of energy and nutrients were calculated from daily dietary recordings These were made by a trained dietitian who observed all meals eaten by the particular subject during the days studied

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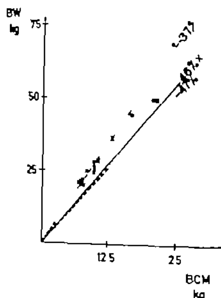


Fig 1. Relationship of body cell mass to body weight in cerebral palsy. As the predicted proportion varies with age (Part V), three approximate identity lines are given, the 37% line for girls above 15 years, the 40% line for boys and girls below 15 years and the 49% line for boys above 15 years. The symbol of each subject indicates the identity line to which he belongs

Body size measurements used for reference include BH and BW as well as derived values, such as surface area and the cubed height. As for the use of the derived values it has been pointed out that often there are no logical reasons why some of these manipulations of data should make them more accurate for reference than the basic observations on which they are based (12)

The active metabolic mass is estimated by such variables as lean body mass, BCM, K and also by basal oxygen requirements. Allometric functions of BCM are also used as reference for growth rates (11)

In order to test if BW is a function of BCM in cerebral palsy it was plotted against BCM, as seen in Fig 1. In normal child population of the corresponding ages BCM can be calculated to be between 37 and 40 per cent of BW (Fig 1 Part V) As seen, most data of the subjects with cerebral palsy indicate a BCM below the predicted proportion

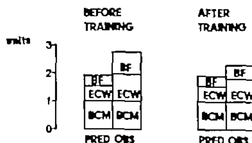


Fig 2. A model of body composition, expressed in units. Subject No 11 Predicted and observed data before and after period of physical training.

Thus in cases of cerebral palsy there will be objections to the use of body size measures, as the condition directly affects body size in a way which varies for different individuals and which cannot be accurately predicted Fig 2 is another illustration of the differences between BW and BCM as reference points in cerebral palsy Regarding FFECS as constant (12 of BW) BW can be approximated to be the sum of the three compartments BCM, ECW and BF (BW) As seen BW changed markedly during the study without a concomitant change in BCM

In order to test if BCM, as the active metabolic compartment is superior to BW for reference in cerebral palsy the oxygen uptake in relation to BCM and BW was studied. The observed maximal oxygen uptake per kg BCM and BW before and after training (data from Part III and Table 2 of the present part) was calculated as per cent of values of healthy children (1) and given in Table 1 If BW is to be adequate as a reference value in general because of its relationship to BCM, it must be possible to correct the BW of children with cerebral palsy for their excess of extracellular mass Each subject is then assumed to have the predicted ECW and BF for his actual BCM instead of the observed ECW and BF[1]) Oxygen uptake per kg corrected BW of children with cerebral

[1]) o = observed, p = predicted, corr = corrected

$BW - FFECS = BW$

$BW = BCM + ECW + BF$

$BW^{corr}_{o} = BCM_{o} + ECW_{p} + BF_{p}$

point in the second simplified study is a new approach The results obtained appear to justify the use of the simplified procedure However a more general application of the simplified method must await a more careful scrutiny of possible different coinciding points in other larger materials

Results

Physical working capacity effect of training (Parts II and III) The observed "maximal" oxygen uptake was limited by muscular in efficiency as evaluated on the basis of a low observed maximal heart rate For this reason *it was not possible to measure the aerobic power or the maximal oxygen uptake as limited* by circulatory factors The observed "maximal oxygen uptake increased after training for vari ous periods in 20 of 22 subjects Twelve had increases of 25 per cent or higher The increase was due to a better muscular efficiency with a mean increase of 9 beats per minute of the ob served maximal heart rate but also to true circulatory effects as found from a higher oxygen uptake at submaximal levels

Lung volumes (Part II) The total lung capacity was significantly reduced averaging 85 per cent of normal values predicted for height The spastic children had a normal distribution of the subdivisions of lung volumes The dys-kinetic group had an abnormal increase in the residual volume to 156 per cent and a vital capacity of 50 per cent of predicted No group demonstrated any signs of airway obstruction.

Body composition and nutrition (Part V) BH *was below the 2.5 per cent population limit* for 7 of 23 subjects BW in relation to height was increased above the 97.5 per cent population limit in 4 of 16 spastics. The mean BCM in rela tion to height was 85 7 per cent ± 7.5 per cent (S E) of predicted TBW was 1 83 kg (predicted 1.34) per kg BCM and ECW was 1 06 (predicted 0.50) kg per kg BCM BF was below predicted in 7 of 8 dyskinetic subjects and in 5 of 15 of the spastic subjects while higher than normal values were found in 7 spastic subjects

Energy intake was often lower than predicted considering age and height but adequate for metabolic size in 11 of 23 subjects. The intake of essential nutrients varied but was low in one or several respects for most subjects. Iron intake was low for all subjects. The protein intake was often adequate

Effect of therapy on body composition (Part VI) Physical training significantly ($p<0.01$) reduced ECW and increased BF ($p<0.01$) The improved nutrition and training combined had a reducing effect on ECW but no significant effects on BF Actually 3 of 7 obese subjects decreased their BF on this regimen The im proved nutrition alone induced no significant *effects on ECW or on BF* BCM was never affected in a significant way except for what could be attributed to growth

The spontaneous physical activity (Part VII) varied greatly in the group studied The varia tions observed agreed well with the intake of energy on the one hand and the nutritional status of body fat amounts on the other

General discussion

1 *Choice of reference values in children with cerebral palsy*

Observations of body functions must be re-ferred to body units to be meaningful Basically two types of reference values are used i e those based on body size measures and those connected with the concept of the active metabolic mass as originally suggested by Benkhe (2) From a theoretical point of view the latter values seem preferable but the dif ficulty of measuring them has limited their use in favour of body measurements It has been suggested (12) that body size measurements are valuable as reference values because the body size is determined to a great extent by the active metabolic mass In homogenous mate rials there would be a close relationship be tween the two types of reference values. In heterogenous materials one must assume that the relationship is not relevant and conse quently the active metabolic mass itself would be the best reference point

of defining obesity in general terms. On the basis of whole body ⁴⁰K counting and determination of TBW or ECW it should be possible to estimate means and standard deviations of BF in kg per kg BCM for different ages and sexes. The normal range of BF in relation to BCM can then be expressed with the standard deviation as unit, making the definition generally applicable.

2. *Physical working capacity*

Comparison with "normal" values. In evaluating the training results it is important to compare the physical working capacity before and after training, with that of healthy children. No reports on maximal oxygen uptake in relation to BCM for healthy children have been published to my knowledge. However it was considered possible to recalculate data related to BW by assuming that a healthy child has a normal body composition, i.e. a predictable percentage of BW = BCM. Data presented by Åstrand (1) were used for such a recalculation and are given in Table 2 as "normal" values together with data of the children with cerebral palsy. Two subjects (Nos. 4 and 14) actually had a normal capacity before training. If the observed values are expressed as per cent of normal values (Table 1), the mean maximal oxygen uptake of the subjects before training was 71 per cent and after training 90 per cent. The mean difference was significant ($p < 0.01$).

TABLE 2. *Maximal oxygen uptake per kg BCM for school children with cerebral palsy before and after training. Normal values for different age groups recalculated from Åstrand* (1)

Subjects		Maximal oxygen uptake ml/min × kg BCM girls	boys
normal 7.5–10 years		*114*	*123*
No. 21	before training	101	
	after training	109	
normal 10–12.5 years		*109*	*125*
No. 1	before training		83
	after training		94
No. 7	before training		82
	after training		138
No. 20	before training		61
	after training		67
normal 12.5–15 years		*109*	*122*
No. 19	before training		106
	after training		118
No. 11	before training		70
	after training		102
No. 14	before training		122
	after training		117
normal 15–17.5 years		*114*	*115*
No. 8	before training	71	
	after training	106	
No. 2	before training		61
	after training		69
No. 15	before training		62
	after training		109
No. 16	before training		76
	after training		120
No. 18	before training	91	
	after training	100	
normal 17.5–22.5 years		*118*	*119*
No. 4	before training		106
	after training		118

The Åstrand material was chosen for comparison, as it was studied with direct determinations of oxygen uptake during work. Compared with data from other countries, Åstrand's subjects have high capacities (14). The conclusion would be that the Åstrand material represents upper strata of healthy children without habitual training. The results obtained with the children with cerebral palsy may be viewed in that light.

Limiting factors. The observed maximal physical working capacity of the material was found to be limited mainly by muscular inefficiency. This was considered the effect of at least two factors: the motor disturbance itself, and the general conditions of living where strenuous physical activity was not encouraged. Malnutrition is also known to cause inactivity and may enforce the two previous mechanisms. The constant activity of the dyskinetic subjects did not seem to induce a higher physical working capacity, as severity of handicap rather than type was correlated to the physical capacity level.

No direct or indirect evidence of circulatory

TABLE 1 *"Maximal" oxygen uptake of CP children as per cent of values of healthy children before and after training Calculations with respect to BCM BW and BW_{-s} corrected for excess of ECW and BF*

Index No	Per kg BCM	Per kg BW	Per kg BW corr
1 *before trai ng*	66	40	63
after training	9	49	78
•	53	3	50
	60	4	59
4	98		9
	100	9	100
	66	53	68
	110	80	109
8	6	0	65
	95	91	96
11	57	39	53
	84	67	83
14	100	77	98
	96	83	97
15	54	48	53
	95	8	9
16	60	60	60
	104	98	103
18	80	75	8
	88	89	85
10	87	0	84
	97	9	95
"0	49	30	49
	54	38	54
1	89		87
	11	60	111
Mean ± 1 S.D			
before	71.3 ± 17 5		
afte	90.3 ± 17 5		
all data	80 8 ± 19 7	66 1 ± 19 8	79 8 ± 19 9
Diff rence ± 1 S.D			
columns 1 and _, and 3		14 7 ± 8 8	−13 8 ± 8 0
t value f the differences		8.96	−8.8
Diff rence ± 1 S.D			
columns 1 and 3			1 0 ± 1 6
t value f the difference			3 28

palsy as per cent of normal values is seen in Table 2 third column As mathematically expected there is a good agreement in this second set of data with oxygen uptake per kg BCM There is however a small but significant difference between the data of columns 1 and 3

This difference may be due to a systematic error in calculation of BW^{corr} with respect to ECW_p and BF_p or FFECS

A study was also made to see if BCM may be preferred to BW as reference value also in healthy subjects *For this end Åstrand's data* (1) of maximal oxygen uptake per kg BW were recalculated to BCM Both sets of data as means *for different age periods are given in Fig 3* The sex difference disappears when BCM is used for reference The inexactness of the re calculated data probably permit no conclusions as to the validity of the age trend

Other reference values based on body size measures were not considered as the abnormal body composition found in this material ruled them out for the same reasons as BW was found less suitable

Consequently it is concluded, that BCM was the superior reference point in cerebral palsy with respect to energy metabolism BCM may be determined directly from K which will be easy when whole body counting is generally available By this method K can be determined from the naturally occurring isotope ^{40}K

In studies of body composition in children, BCM is also the preferable reference value as discussed in Part V Changes in body composition due to growth of cell mass can be separated from therapeutic effects if the compartment studied is expressed in kg per kg BCM Relating BF to BCM gives a possibility

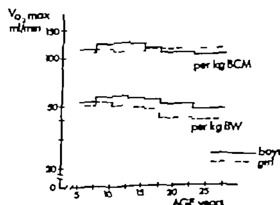


Fig 3 Maximal oxygen uptake of healthy subject (1) t different age periods, referred t body cell mass and to body weight.

of defining obesity in general terms. On the basis of whole body ⁴⁰K counting and determination of TBW or ECW it should be possible to estimate means and standard deviations of BF in kg per kg BCM for different ages and sexes. The normal range of BF in relation to BCM can then be expressed with the standard deviation as unit, making the definition generally applicable.

2. *Physical working capacity*

Comparison with "normal" values. In evaluating the training results, it is important to compare the physical working capacity before and after training, with that of healthy children. No reports on maximal oxygen uptake in relation to BCM for healthy children have been published to my knowledge. However, it was considered possible to recalculate data related to BW by assuming that a healthy child has normal body composition, i.e. a predictable percentage of BW as BCM. Data presented by Åstrand (1) were used for such a recalculation and are given in Table 2 as "normal" values together with data of the children with cerebral palsy. Two subjects (Nos. 4 and 14) actually had a normal capacity before training. If the observed values are expressed as per cent of normal values (Table 1), the mean maximal oxygen uptake of the subjects before training was 71 per cent and after training 90 per cent. The mean difference was significant ($p<0.01$).

The Åstrand material was chosen for comparison, as it was studied with direct determinations of oxygen uptake during work. Compared with data from other countries, Åstrand's subjects have high capacities (14). The conclusion would be that the Åstrand material represents upper strata of healthy children without habitual training. The results obtained with the children with cerebral palsy may be viewed in that light.

Limiting factors. The observed maximal physical working capacity of the material was found to be limited mainly by muscular inefficiency. This was considered the effect of at least two factors: the motor disturbance itself and the general conditions of living where strenuous physical activity was not encouraged. Malnutrition is also known to cause inactivity and may enforce the two previous mechanisms. The constant activity of the dyskinetic subjects did not seem to induce a higher physical working capacity, as severity of handicap rather than type was correlated to the physical capacity level.

No direct or indirect evidence of circulatory

TABLE 2. *Maximal oxygen uptake per kg BCM for school children with cerebral palsy before and after training. Normal values for different age groups recalculated from Åstrand (1)*

Subjects	Maximal oxygen uptake ml/min × kg BCM girls	boys
normal 7.5–10 years	*114*	*123*
No. 21 before training	101	
after training	109	
normal 10–12.5 years	*109*	*125*
No. 1 before training		83
after training		99
No. 7 before training		8
after training		138
No. 20 before training		61
after training		67
normal 12.5–15 year	*109*	*122*
No. 19 before training		104
after training		118
No. 11 before training		70
after training		102
No. 14 before training		121
after training		117
normal 15–17.5 years	*114*	*115*
No. 8 before training	71	
after training	109	
No. 2 before training		61
after training		69
No. 13 before training		62
after training		109
No. 16 before training		76
after training		120
No. 18 before training	91	
after training	100	
normal 17.5–22.5 years	*116*	*110*
No. 4 before training		109
after training		118

TABLE 1 *"Maximal" oxygen uptake of CP children as per cent of values of healthy children before and after training Calculations with respect to BCM BW and BW ₛ corrected for excess of ECW and BF*

I dex N	Per kg BCM	Per kg BW	Per kg BW corr
1 before trai i g	60	40	03
after trai i g	79	40	8
	53	37	50
	60	4	59
4	98		97
	100	9	100
7	66	53	66
	110	86	100
8	6	6	65
	95	91	96
11	57	39	53
	84	67	83
14	100	—	98
	96	83	9
15	54	48	53
	95	87	9
16	66	60	66
	104	98	103
18	80	5	8
	88	89	85
19	87	70	84
	97	9	95
*0	49	30	40
	54	38	54
1	89	7	87
	11	89	111

Mean ± 1 S D			
before	71 3 ± 17.5		
after	90.3 ± 17 5		
all data	80 8 ± 19 7	66 1 ± 19.8	79 8 ± 19 9
Diff rence ± 1 S.D			
columns 1 and , and 3		14 7 ± 8 8	− 13 8 ± 8 0
t value for the lifferences		8 90	− 8 8
Difference ± 1 S D			
columns 1 and 3			1 0 ± 1 6
t value fo the difference			3 *8

palsy as per cent of normal values is seen in Table 2 third column As mathematically ex pected there is a good agreement in this second set of data with oxygen uptake per kg BCM There is however a small but significant dif ference between the data of columns 1 and 3 This difference may be due to a systematic error in calculation of BW corr with respect to ECW_p and BF_p or FFECS

A study was also made to see if BCM may be preferred to BW as reference value also in healthy subjects For this end Åstrand s data (1) of maximal oxygen uptake per kg BW were recalculated to BCM Both sets of data as means for different age periods are given in Fig 3. The sex difference disappears when BCM is used for reference The inexactness of the recalculated data probably permit no conclusions as to the validity of the age trend.

Other reference values based on body size measures were not considered as the abnormal body composition found in this material ruled them out for the same reasons as BW was found less suitable

Consequently it is concluded that BCM was the superior reference point in cerebral palsy with respect to energy metabolism. BCM may be determined directly from K which will be easy when whole body counting is generally available By *this method* K *can be determined* from the naturally occurring isotope ^{40}K

In studies of body composition in children, BCM is also the preferable reference value as discussed in Part V Changes in body com position due to growth of cell mass can be separated from therapeutic effects, if the compartment studied is expressed in kg per kg BCM Relating BF to BCM gives a possibility

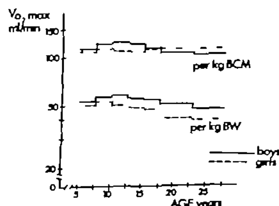


Fig 3. Maximal oxygen uptake f healthy subject (1) t different age periods, referred t body cell mass and to body weight

3. *Lung volumes*

If the lung volumes of the subjects reported in Part IV are related to BCM, and if the predicted normal values are recalculated to the same reference value by assuming a normal body composition in the healthy subjects the difference between observed and predicted values of total lung capacity no longer becomes significant ($p>0.05$). The total size of the lung parenchyma can hardly be directly affected by cerebral palsy There are various reasons, however why cerebral palsy may reduce BCM (Part V). For this reason, it seems logical to conclude that the total lung capacity has developed in response to the metabolic need of the cells.

The vital capacity can also be recalculated with BCM as a reference point. In this connection, however there is still a significant difference ($p<0.01$) between observed and predicted values. Thus, these recalculations have confirmed the observation of an abnormal vital capacity in cases of cerebral palsy

A total lung capacity which is adequate for the metabolic size can hardly be expected to interfere with the physical working capacity It is possible however that a low vital capacity may be limiting factor and the correlation between the observed maximal oxygen uptake before training and vital capacity was studied There was a significant correlation with a coefficient of 0.60 which may mean that poor ventilatory capacity can limit some subjects

4. *Mean daily energy expenditure*

In Part VII the mean daily energy expenditure is given for 10 subjects as kcal per 24 hours For comparison between different individual these dat were converted to mean oxygen uptake in ml per min te per kg BCM and plotted against age as seen in Fig. 6 The mean daily spontaneous activity is said to decrease with age Moreover a small body has a proportionally larger surface area than a big body One reason for having a higher metabolic turnover per unit BCM would then be to keep

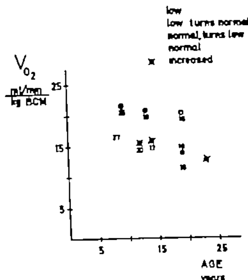


Fig. 6. Mean daily energy expenditure (oxygen uptake in ml per minut per kg BCM) correlated to age Each point carries the subject index number and also indicates his body fat level.

a constant temperature This would tend to give a higher mean oxygen uptake per unit BCM in younger and smaller subjects. The general trend of the data in Fig 6 also supports this assumption.

Inactivity is said to be an important factor for provoking obesity and probably is more common than excessive energy intake (18) Since the data in Fig 6 seem to refer to different levels of activity the state of BF and the dynamic changes during the last half year preceding the determinations of activity (data of Table 3 Part VII) are indicated for each subject Five subjects, who are obese or normal and remain so appear to have a level of activity distinctly lower than that of subjects, who are or turn slender This may indicate that the habitual level of activity is of importance for the BF amounts. The data may also be compared with the predicted activity level given in Table 5 Part V

The individual variations found in our material may be considered small, however viewed in the light of general metabolic laws of energy expenditure in human beings. Energy expenditure per 24 hours is probably a function of the

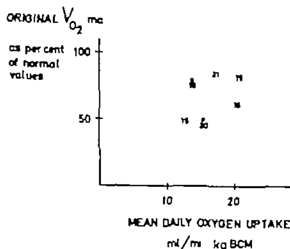


Fig 4 Mean d ily energy expenditure and the initially bserved maximal oxygen uptake

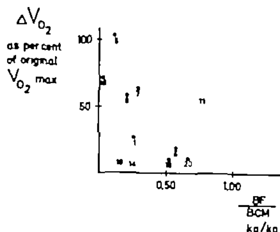


Fig 5. Body fat as kg per kg body cell mass (normal range 0 *6–0 44) and the trainability (increase of observed "maximal oxygen uptake as per cent of initially observed maximum).

abnormalities which could cause an early lim itation of physical work was found The abnormal lung function giving abnormal volume distribution in the dyskinetic subjects may be a potential limiting factor A significant correlation was also found between vital capacity and maximal observed oxygen uptake However the role of the lung in limiting maximal work in subjects with cerebral palsy cannot be settled on the basis of the data available so far

Causes of the low capacity It is not unlikely that the neuromotor disturbance itself can be one cause of the reduced physical working capac ity as it prevents the subject from performing vigorous quick or strong movements of many parts of the body at the same time The mean observed "maximal oxygen uptake in spastic subjects before training was 67±10 (S D) per cent of normal values In the dyskinetic subjects the uptake was 81±10 (S D) per cent This difference is non-significant and indicates that the type of tonus disturbance may not be im portant in reducing the physical working capac ity The severity of the handicap however was shown to be important as the mean capacity of Grade 3 subjects (scale 1–3) was 58±7 (S D) per cent of normal values and of Grade 2 subjects 87±13 per cent The means between the two groups differed significantly ($p<0\ 01$) as tested with Student s *t* test

The physical working capacity before training and the trainability showed no evident correlation to the mean daily spontaneous activity (Fig 4) and no correlation to BF (Fig 5)

The trainability was not affected by the type of the tonus disturbance nor by the severity of the affliction as the mean improvement was similar in the different categories.

Conclusions The causes of the low physical working capacity in this material are probably many and interrelated It is obvious that the handicap itself particularly the severity of it is one cause The level of habitual activity is generally a factor of importance but its import ance in this material cannot be stated (Fig 4) The fact that the success of the training was not correlated to the type the severity of the handicap or to the spontaneous activity must indicate that the general management of the subjects did not favour the development of a good physical capacity The effect of the train ing i e the increase in the observed maximal heart rate of the subject (Part III) is probably the best single expression of the fact that the subjects were not given enough opportunities for vigorous physical activities. However the effects of physical training which raised the physical capacity to 90 per cent of the maximal oxygen uptake of healthy subjects, indicate that all round training of muscles and circulation is well motivated in addition to the special physiotherapy needed by these subjects.

3. Lung volumes

If the lung volumes of the subjects reported in Part IV are related to BCM, and if the predicted normal values are recalculated to the same reference value by assuming normal body composition in the healthy subjects, the difference bet een observed and predicted values of total lung capacity no longer becomes significant ($p>0.05$) The total size of the lung parenchyma can hardly be directly affected by cerebral palsy There are various reasons, how ever why cerebral palsy may reduce BCM (Part V). For this reason, it seems logical to conclude that the total lung capacity has developed in response to the metabolic need of the cells.

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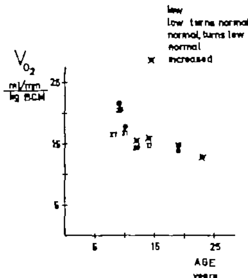


Fig 6 Mean daily energy expenditure (oxygen uptake in ml per minute per kg BCM) correlated to age Each point carries the subject index number and also indicates his body fat level.

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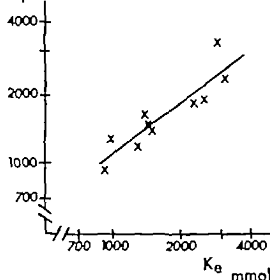


Fig 7 Mean daily energy expenditure (kcal per 24 hours) correlated to total body potassium The regression line is given

total active metabolic mass or K (22) A linear relation with a significant correlation coefficient of 0 85 between energy expenditure and K was also found in our ten subjects. However it has been suggested that the function is exponential (16) A linear relationship of the data was also found in a double logarithmic scale Fig 7 In this case the correlation coefficient was 0 90 There is however no significant difference between the two correlation coefficients The reason for the good fit of our material to both ways of plotting is probably that the material covers just a small section of body sizes

5 *Body composition*

A few longitudinal studies of body composition in children based on isotope dilution methods are available (13) No reports of such studies are found in children with cerebral palsy however

Malnutritive changes with a reduced BCM and increased ECW were demonstrated The dietary recordings revealed that the subjects could not satisfy their need for essential nutrients within the limits set by the low energy need Thus dietary defects and low activity could be responsible for the malnutrition

In the longitudinal studies, improved nutrition and physical training caused significant changes in ECW and in BF But the effects of improved nutrition and of physical training could not be separated from each other in the studies There was however some indication that the introduction of physical activation alone was more potent than introduction of a better diet alone One cause for this seemed to be that physical training as the only introduced change, by itself involved a better nutrition because of an increased food intake

The absence of growth spurt after therapy and the lacking effects on ECW after nutritional therapy alone indicate that the observed malnutrition was not severe

All nutritive defects were not corrected within the low limits set by the energy requirements in these subjects due to individual taste and food preference Iron often remained below the recommended amounts A general goal of nutritional science is to avoid supplements but for this particular group supplements of iron must be considered

Even though improved nutrition and increased physical activation affected body composition favourably a complete normalization was not achieved and the ultimate result is not known. Further studies in these fields are necessary particularly on younger subjects.

In this section the attention will be drawn to a cellular aspect of the disturbed body composition Fig 2 shows that the relationship between extra and intra cellular mass may be greatly disturbed in a subject with cerebral palsy All 23 subjects studied had an abnormally high extra cellular mass (ECW+BF)—even those where BW was below predicted The implication of this cannot be generalized as being good or bad One consequence however must be that the distance for transportation of metabolites to and from the cells is longer than normal Moreover the metabolic load on the cells to support their environment must be greater In Subject No 11 Fig 2 therapy decreased the extracellular mass. A further analysis of the effects of training and of im

proved nutrition on the extracellular mass was performed in all subjects with the sign test (Data from Tables 6–16 of Part VI.) The over-all effect in all subjects during the total observation period of any type of therapy was a reduction of extra-cellular mass in 15 of 18 subjects, which means that the effect was significant ($p<0.01$)

Favourable training results and improved nutrition must not, however involve a reduction of both compartments. As BF and ECW differ greatly in function and distribution, it may not be correct to combine them when evaluating the extracellular load. Water is generally distributed in the body and thus ECW alone may be an adequate expression of the relation between cells and the environment. Even so, an excess of extra-cellular water may show an abnormal distribution as found in some pathological conditions (10)

6 *Somatic differences between spastic and dyskinetic subjects*

T types of abnormal muscular tonus, spasticity and dyskinesia, were considered major clinical differences in the present material. It may be of value to study if the disturbances found ere different in the two main groups

No statistically significant difference was found when comparing the original *maximal* oxygen uptake between spastic and dyskineti subjects, and the effect of training was also similar in the tw groups Lung volumes dif fered, as the dyskineti subjects had an abnormal volume distribution in the lungs with an abnormally increased residual volume After physical training only the dyskinetic subjects exhibited an improved muscular control (7) Body composition disturbances were equal in the t groups but differed quantitatively in body fat amounts. All dyskinetic subjects had low BF while spastic subjects demonstrated great variations.

The difference in neuromotor disturbances was the probable cause of the lung volume difference and of the improved voluntary control after exhaustion, as these two observations were made only in dyskinetic subjects. The low body fat in all dyskinetic subjects was probably caused by a high energy expenditure of that group as no difference was noted in energy intake between the two groups Obviously how ever some spastic subjects can also have a high energy expenditure.

7 *Adaptation*

As the main abnormality in body composition and the low physical capacity were not closely related to the type of neuromotor disturbance the severity of the disability may be the com mon factor The severity probably limits the activity of the child The constant motions of some dyskinetic subjects are energy-consuming, but probably do not stimulate the development of a good physical working capacity or an increased—or even normal—BCM The in stitutional care itself was not a probable cause, as the children did not improve during vacations at hom However as training and improved nutrition could decrease the deviations in body composition and increase the physical capacity of the subjects the general management of the children is a factor of importance

It can be claimed that stricter enforcement of the diet may have yielded better results. Also the physical training program could have been more efficient. Such an approach was not attempted, however out of fear for the negative reactions that rigid therapeutic regimens are bound to provoke Even with a soft approach, there were some signs of food distaste and of less enthusiasm for the training during the second year of study This probably indicates that the challenge in the proper management of these children is to avoid strict routine. By offering variety with respect to food and to physical activities, it should be easier to satisfy individual preferences. Thus, activity and improved nutrition could become a normal way of life for the child with cerebral palsy and not a therapeutic regimen.

Summary

Fourty-one school children with severe affliction of cerebral palsy participated in one or more studies on adaptory mechanisms in cerebral palsy

The studies dealt with the physical working capacity lung volumes body composition, nutrition and spontaneous activity Effects of therapy with physical training and improved nutrition were also studied.

Data from the different studies were integrated and gave the following results

The abnormal body composition during growth directly affects body weight (BW) For this reason body cell mass (BCM) representing the active metabolic mass is suggested as the reference value for subjects with cerebral palsy with respect to metabolic data including gross body composition

The mean physical working capacity before training was 71 per cent of that of healthy children per kg BCM The main limits to maximal work were considered muscular The severity of the handicap appeared to be the factor most closely related to the original low working capacity of the factors studied

The physical working capacity significantly increased to a mean of 90 per cent of normal values

The total lung capacity was reduced when compared to the predictions for height (BH) but adequate when correlated to BCM The subjects with dyskinetic cerebral palsy had an abnormal volume distribution of air with increased residual volume

Malnutritive changes were found in the body composition with a decrease of BCM to 85 per cent of the prediction for BH and with an increase of extracellular water (ECW) from a predicted mean of 0 56 per kg BCM to 1 06 In addition 7 of 23 subjects had a BH below the 2.5 per cent population limit for age The physical training alone and in combination with an improved nutrition significantly reduced ECW but did not effect BCM BF was significantly increased by training only Improved nutrition alone had no significant effects, which indicated that the malnutrition was not severe The increased extracellular mass (ECW+BF) may cause a metabolic load on the cells and abnormal conditions for transport

The spontaneous physical activity correlated well with total body potassium (K BCM) Factors which may modify the habitual activity such as age and BF were studied

The difference in neuromotor disturbance between the spastic and the dyskinetic group caused minor differences concerning volume distribution of air in the lungs voluntary control of movements after exhaustion and body fat amounts

The severity of handicap was found to be of importance in causing unspecific somatic complications The motor disability restrains the physical activity and creates subjects with a low energy need The consequences of this can be softened by a proper management which provides a variety of physical activities and a diet with a high content of essential nutrients per unit energy

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From the Department of Pediatrics and the Department of Plastic and Reconstructive Surgery

University of Bergen, Bergen, Norway

CLINICAL AND CYTOGENETIC STUDIES IN HYPOSPADIAS

by

Dagfinn Aarskog

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Introduction

Recent advances in experimental embryology cytogenetics and steroid biochemistry have accumulated considerable information on the mechanisms of sex determination and differentiation. These data have substantiated the classical concept that most sexual characteristics emerge from bivalent or indifferent precursors in the embryo, and that a wide spectrum of differentiation is possible at each level of sexual organization.

The genetic sex of most mammals is determined at fertilization when either an X bearing or a Y bearing sperm unites with an X bearing ovum to form a zygote with either an XX or an XY sex chromosome constitution.

The gonadal sex is determined when the early indifferent gonad develops into a testis or an ovary. The presence or absence of normal Y chromosome is apparently a decisive factor at some critical stage in this differentiation. If a Y chromosome is present, testes normally develop. If there is no Y chromosome, an ovary results.

The phenotypic sex depends upon the differentiation of the genital ducts and external genitalia and, according to the experiments of Jost (58) it is primarily influenced by the fetal testes. During the indifferent stage of intrauterine life, the fetus is equipped with primordia of both male and female ducts. The Mullerian ducts, or oviducts, serve as the anlage of the Fallopian tubes, uterus and the upper portion of vagina, whereas the Wolfian, or mesonephric ducts, are capable of differentiating into the epididymus, vas deferens and seminal vesicles. The two sets of ducts are similar in human embryos throughout the second month of pregnancy. During the third fetal month either the Müllerian or Wolfian ducts complete their development while regression of the heterologous ducts occurs simultaneously. On the basis of embryonic castration experiments in the rabbit, Jost elaborated the theory that secretions from the fetal testes play a decisive role in determining the direction of genital duct development. Bilateral castration of males resulted in retrogression of the Wolfian ducts, with persistence of Müllerian duct derivatives. In castrated females, the Wolfian ducts disappear and Müllerian ducts differentiate as in normal females. The influence of the fetal testis on duct development is exerted unilaterally since early removal of one testis leads to persistence of Müllerian derivatives on that side, while the male duct develops normally on the side on which the testis remains intact.

The development of the external genitalia is the last phase of embryonic sex differentiation to be completed. At the eighth fetal week, the external genitalia of both sexes are identical and have the capacity to differentiate in either direction. The difference between the male and female genitalia depends upon the degree of development of the phallus and the extent of the fusion in the midline of the urethral groove and labioscrotal folds. As in the case of the genital ducts, there is an inherent tendency for the external genitalia to feminize and differentiation along male lines will occur only if male

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ness is imposed by the fetal testes during the critical stages of masculinization.

The normal differentiation of the gona ducts and external genitalia thus depends chiefly upon *substances secreted by the* fetal testes These substances fall into two categories one causing regression of the Müllerian ducts, and the other causing male development of Wolfian ducts and masculinization of external genitalia. Known androgenic hormones can mimic the latter effect but do not inhibit devel opment of the Müllerian ducts (60)

The experiments by Jost in the rabbit fetus have shown that the results of an impairment in fetal testicular function depend on two factors the stage of sexual differentiation and the degree of testicular impairment Bilateral castration of a male fetus at an early stage resulted in entirely female development of the genital ducts and external genitalia whereas a reduc tion of testicular secretory activity produced by decapitation of the fetus, at a late stage only resulted in hypospadias. Accordingly Jost regards hypospadias as a mild form of male pseudohermaphrodit ism (57 58) Male pseudohermaphrodit ism is by definition a condition in which the gonads are testes but in which there *are either gross remnants of Müllerian* structures, or the appearance of the external genitalia is ambiguous enough to give rise to uncertainty as to the sex. It appears that the division between simple hypospadias and male pseudohermaphroditism is rather arbitrary

Although the results of experimental embryology indicate that hypospadias might result from deficient fetal testicular function, the general attitude of the pediatrician has been to regard the condition merely as a malformation of unknown etiology and mainly a problem of reconstructive surgery The aim of the present study has been to investigate a material of hypospadic patients with special reference to pathogenetic mech anisms which might have interfered with *testicular differentiation and/or function* during fetal life

Subjects

The material consists of 80 hypospadic patients. All of them had been reared as boys. The majority of patients, 71 cases, were ascertained through reference to the Department of Plastic and Reconstructive Surgery for repair of the hypospadias. The remaining cases were first seen in the Department of Paediatrics for evaluation of the urogenital anomaly In the latter group there was one patient with an intersex condition (case 5) Patients in which the hypospadias was only a part of multiple congenital anomalies were excluded from the study One patient with a penil hypospadias had a similarly affected brother Otherwise there was no case of hypospadias among close relatives.

The hypospadias was classified into four categories according to the position of the urethral meatus

Glandular hypospadias with meatus situated at, or close to the coronal sulcus.

Penile hypospadias with the urethral orifice between the coronal sulcus and the penoscrotal angle.

Penoscrotal hypospadias with the urethral opening in the penoscrotal angle.

Scrotal hypospadias in which the urethral meatus opens on a clefted or bifid scrotum

There was no case of perineal hypospadias. Cordae, to various extent, with associated ventral-curvature of the penis were present in all cases. Both testes were present in the scrotum in 70 cases. In 8 cases only one testis was descended and in the remaining 2 cases there was bilateral cryptorchidism. The distribution of patients according to the type of hypospadias and position of the testes is shown in Figure 2.

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Methods

1 Cytogenetic investigation

Chromosome analysis was carried out in cultures from whole capillary blood and bone marrow. Cultures were set up by adding 3 drops of blood or bone marrow aspirate to 7 ml of tissue culture medium made up of 6 ml Difco T C 199 medium and 1 ml human AB serum. Bone marrow cultures were processed immediately and after incubation at 37°C for 24 hours following the addition of 0.1 ml phytohaemagglutinin. Capillary blood cultures were incubated for 3 days.

As a routine 30 to 50 metaphases were examined. The probability that a random sample of cells from a mosaic subject with two cell lines will not include at least one cell of the minor cell line that is present in a given frequency is expressed by (1-p) where p is the frequency of the cell line in question and n the number of cells in the sample. For samples of 30 and 50 cells and for a frequency of 0.05 the probabilities are 0.214 and 0.077 respectively. It can be inferred that, if the cell line comprises only 5 per cent of the cells in the population, it would pass unsuspected approximately once in 5 trials if the sample size were 30 cells, and approximately once in 12 trials if the sample were increased to 50 cells.

If the routine examination aroused suspicion of a mosaic condition the number of metaphases examined was increased until, eventually the number of recorded cells from the minor cell line was higher than could reasonably be attributed to chance. Unfortunately strict statistical criteria for the acceptance of a hypomodal cell line as an expression of mosaicism cannot be applied (31). However when the cytogenetic evidence for the diagnosis of mosaicism was not sufficiently striking for acceptance without question, analyses were repeated on three different occasions in cultures from capillary blood and also performed in cultures from bone marrow. In these instances mosaicism was only accepted when the hypomodal cell line was consistently found in repeated cultures.

2 Hormone analyses

Testosterone in the urine was determined by the use of displacement analysis according to the method of Stoa and Thorsen (107). The principle of this method is to measure testosterone by means of competitive binding to the testosterone binding protein in serum from pregnant women. In order to correct for methodological losses an internal standard of 1,2 ^{3}H testosterone was added to the urine sample. Following extraction from the urine testosterone was isolated and purified by paper chromatography in the system n hexane benzene (2 1) for mamide and on silica gel thin layer with benzene ethyl acetate (1 1). Dextran coated charcoal particles were added to the incubation mixture to separate bound and free testosterone.

The method used for estrogen analysis has been described in detail by Stoa and Thorsen (106). Briefly it entails hydrochloric acid hydrolysis ether ex

traction, solvent partition in benzene/light petroleum/0.25 N sodium hydroxide, followed by aluminia column chromatography. After elution, the estrogens were measured fluorometrically employing a modification of the Ittrich method.

Follicle stimulating hormone (FSH) was measured by the mouse uterine augmentation test. The method involves the extraction of 200 ml urine by the tannic acid procedure. The extracts were injected together with a priming dose of 0.3 I.U. human chorionic gonadotropin (105). It is believed that this procedure measures FSH specifically and that luteinizing hormone (LH) does not contribute significantly to the result (9). The results have been expressed in I.U. with reference to the 2nd I.R.P.

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Results

1 Maternal treatment with progestins

All mothers were asked about drug ingestion during the first trimester of pregnancy A history of progestin usage was elicted in 5 mothers. Their infants presented with hypospadias which varied in degree from the distal penile type to the penoscrotal form The type of drug and dosage was confirmed in 4 cases by the recovery of the prescription and/or statements from the mothers physicians (Fig 1) Progestin was used because of threatened abortion in 2 cases (medroxyprogesterone and hydroxyprogesterone caproate) In the other 3 cases progestin was used for the purpose of a pregnancy test. In two of these instances norethisterone was used either alone or in combination with ethinylestradiol In the third case the exact nature of the progestin is unknown, but most probably it was either medroxyprogesterone or norethisterone. When used in pregnancy testing progestin was given on two successive days. Hydroxyprogesterone caproate was administered intramuscularly in one injection on the

HYPOSPADIAS ASSOCIATED WITH MATERNAL TREATMENT WITH PROGESTINS

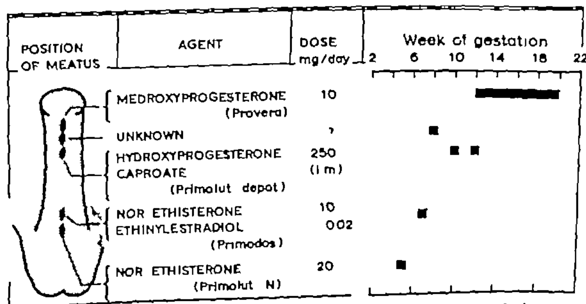


Fig 1 Note relationship between the position of the urethral meatus and the week of gestation at which maternal progestin treatment was started

THE RELATIONSHIP OF EXTERNAL GENITALIA TO THE SEX CHROMOSOME CONSTITUTION IN 80 CASES OF HYPOSPADIAS

TYPE OF HYPOSPADIAS \ GONADS			
	NUMBER OF CASES & SEX CHROMOSOMES		
	31 xy	1 xy	
	21 xy	2 xy	1 xx
	10 xy 2 xx/xy	4 xy 1 xo/xy	1 xx/xy
	5 xy 1 xo/xy		

Fig Abnormal sex chromosome complements tended to occur in patients with the severest degrees of hypospadias and especially when associated with undescended testes.

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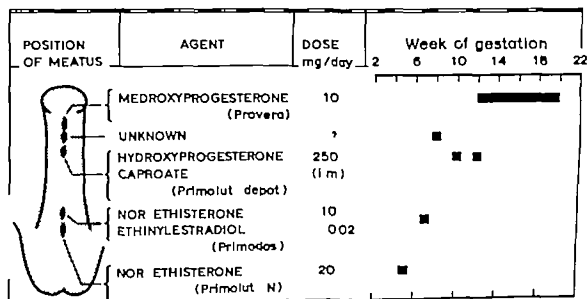


Fig 1 Note relationship between the position of the urethral meatus and the week of gestation at which maternal progestin treatment was started.

T ble 2. *Urinary testosterone and estrogen excretion before and after gonadotropin stimulation*

Subjects	Age (yrs.)	Sex chromosome complement	Intersex condition	Testosterone µg/24 hrs.	Estrogens µg/24 hrs.		
					Estradiol	Estrone	Estriol
Case 1	*11*	XX/XY	Mixed gonadal dysgenesis	5.6 (1 0)	0 4 (0.9)	0 6 (0 7)	1.3 (1.5)
Case 2.	4 6/12	XX/XY	Male pseudohermaphrodit	1.3 (2.6)	0.3 (0.3)	0.2 (0.3)	0.9 (0.8)
Case 3.	7	XX/XY	Mal pseudohermaphrodit	8 7 (5.5)	0.5 (0 4)	0.6 (0.6)	1 6 (0.9)
Case 4	9	XO/XY	Male pseudohermaphrodit	0 4 (1 4)	0.9 (0.8)	*0.9 (0 7)*	2 7 *(1 9)*
Case 5.	1 9/12	XO/XY	Male pseudohermaphrodit	0.2 (2 1)	0.3 (0.2)	0 1 (0 1)	0 4 (0.9)
Case 6	12	XY	Mixed gonadal dysgenesis	7 7 (4 9)	2 0 (0 8)	2.2 (0 8)	1.8 (2 4)

Open *figures* represent basal values. Figures in brackets represent values after HCG administration, 1500 I U twice weekly for 3 weeks and suppression of the adrenal cortex with 2 mg of dexamethasone for the last two days of the treatment period.
Values after *castration and stimulation with human pituitary FSH*, 5 mg daily for 5 day and suppression of adrenal cortex.

10th and 12th week of gestation. The other drugs were given orally

When the position of the urethral meatus was compared to the week of gestation at which progestin treatment was started there seemed to be a relation ship with the more proximal openings in the infants of mothers who had been treated in the first month of pregnancy (*Fig 1*)

2 Cytogenetic findings

The cytogenetic findings are presented in Figure 2 A normal male karyotype was found in 74 cases. Among the remaining 6 cases there were 3 patients with XX/XY mosaic, 2 patients with an XO/XY mosaic, and one patient showed a normal female karyotype The latter patient had congenital virilizing adrenal hyperplasia (case 7)

It will be noted that all cases of glan dular hypospadias had normal male karyotype, and that the abnormal karyotypes tended to occur among the patients with the severest degrees of hypospadias and especially when associated with undescended testes However it is to be emphasized that there were 3 mosaic patients with both gonads present in the scrotum.

A normal male karyotype was found in one patient with mixed gonadal dysgenesis who presented with a penoscrotal hypospadias and unilateral cryptorchidism (case 6)

The results of chromosome analysis in the XX/XY mosaic patients are depicted in Table 1 The XY clone was in minority in all these patients and only one of them was sex chromatin positive in buccal smears.

3 Hormone analysis

The results of hormone analysis in the six male patients with intersex conditions are listed in Tables 2 and 3

Urinary excretion of testosterone and estrogens was measured before and after the administration of 1500 I U of human chorionic gonadotropin (HCG) twice weekly for 3 weeks. To suppress the adrenal cortex, 2 mg of dexamethasone was given for the last two days of the treatment period

The base values for estrogens were within normal range for age and did not increase following HCG stimulation (Table 2)

The mean urinary excretion of testosterone under basal condition was 4 0 ± 3 8 µg per 24 hours (Table 2) In 13 normal prepubertal boys the mean value was 2.3 ± 1 7 µg per 24 hours (range 0 4 to 6.2 µg) There was no significant difference between these mean values

Table 1 *Results of chromosome analysis in 3 cases of XX/XY mosaicism*

Subjects	Source	Number of cultures	Number of XX cells	Number of XY cells	Per cent XX cells	Sex chromatin
Case 1	Blood	3	6	109	5.2	+ (Pos.) 13 Per cent
	Bone marrow	1	4	71	5.3	
Case 2	Blood	3	25	205	10.9	— (Neg.)
	Bone marrow	1	11	88	11 1	
Case 3	Blood	3	15	201	7 0	— (Neg.)
	Bone marrow	1	9	91	9 0	

Table 2. *Urinary testosterone and estrogen excretion before and after gonadotropin stimulation*

Subjects	Age (yrs.)	Sex chromosome complement	Intersex condition	Testosterone µg/24 hrs.	Estrogens µg/24 hrs.		
					Estradiol	Estrone	Estriol
Case 1	11	XX/XY	Mixed gonadal dysgenesis	5 6 (1.0)	0 4 (0.9)	0 6 (0 7)	1.3 (1.5)
Case 2	4 6/12	XX/XY	Male pseudohermaphrodite	1.3 (2.6)	0.3 (0.3)	0.2 (0.3)	0 9 (0.8)
Case 3.	7	XX/XY	Male pseudohermaphrodite	8 7 (5.5)	0.5 (0 4)	0 6 (0.6)	1 6 (0.9)
Case 4	9	XO/XY	Male pseudohermaphrodite	0 4 (1 4)	0.9 (0 8)	0.9 (0 7)	2 7 (1 9)
Case 5.	1 9/12	XO/XY	Male pseudohermaphrodite	0.2 (2 1)	0.3 (0.2)	0 1 (0 1)	0 4 (0.9)
Case 6.	12	XY	Mixed gonadal dysgenesis	7 7 (4.9)	2 0 (0.8)	2.2 (0.8)	1.8 (2 4)

Open figures represent basal values. Figures in brackets represent values after HCG administration, 1500 I U twice weekly for 3 weeks and suppression of the adrenal cortex with 2 mg of dexamethasone for the last two day of the treatment period.

Values after castration and stimulation with human pituitary FSH 3 mg daily for 5 day and suppression of adrenal cortex.

10th and 12th week of gestation The other drugs were given orally

When the position of the urethral meatus was compared to the week of gestation at which progestin treatment was started there seemed to be a relation ship with the more proximal openings in the infants of mothers who had been treated in the first month of pregnancy (Fig 1)

2 Cytogenetic findings

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Case Histories

Case 1. This patient was an 11-year old cryptorchid boy who had surgical correction for a peno-scrotal hypospadias at the age of 4 years. He was the third child of a 38-year old mother and a 37-year old father. The pregnancy was uneventful. The motor and mental development were normal and school achievements were quit satisfactory.

H. was readmitted when 11 years old for further studies. His height was 149 cm (75th–90th percentile) and weight 37.5 kg (25th–50th percentile). H. was well proportioned and no anomalies were noted except for slight cubitus valgus (Fig. 3). There was no secondary sexual development. Reconstructive surgery had resulted in a penis of fairly normal appearance which measured 4 × 2 cm. The scrotum was hypoplastic and no gonads could be palpated. No vaginal remnant was found on urethrocystography. The bone age (Greulich and Pyle standard) corresponded with chronological age. Buccal smears revealed 13 per cent sex chromatin positive cells. Chromosome analyses carried out in cultures from peripheral blood and bone marrow showed 46,XX/46,XY mosaic (Table 1). The results of hormone analyses are depicted in Tables 2 and 3.

Exploratory laparotomy revealed a uterus in the midline measuring about 4 × 3 cm. There were also bilateral tubelike structures extending from both cornua (Fig. 4). On the right side there were no fimbriae and the tube ended nearby a gonad which was located in the expected position of an ovary. However the gross appearance of this gonad was that of a testicle with an epididymus. The left tube presented a fimbriated end but careful examination on this side revealed no gonad. Uterus, both tubes and the testis were removed.

Microscopic examination of the testis showed no evidence of spermatogenesis, and Sertoli cells were the only recognizable tubular elements (Fig. 5). There was some hyalinization of the basement membrane and the interstitial tissue contained groups of well differentiated Leydig cells. Scattered foci of calcification were also noted. Sections through the right tube-like structure proved this to be vas deferens, whereas the left tube had the microscopic appearance of an immature Falloplan tube (Fig. 6). The uterine cavity was lined with a well-differentiated squamous epithelium.

Diagnosis: XX/XY mixed gonadal dysgenesis.



Fig. 3. *Case 1.* Full view of the patient at 11 years of age showing slight cubitus valgus and hypoplastic external genitalia.

Table 3 *Urinary excretion of FSH*

Subjects	Sex chromosome	Spermatogenesis	Age (yrs.)	FSH units
Case 1	XX/XY	Absent	3 9/12 11 11	4 M.U 24 I.U 13 I U *
Case 2	XX/XY	Absent	4 6/12	11 I U
Case 3	XX/XY	Present	7 7	<6 I.U <7 I U
Case 4	XO/XY	Present	9 9	<7 I.U <4 I U
Case 5	XO/XY	Present	1 9/12	<1 I U
Case 6.	XY	Present	12 12 4/12	<8 I U <5 I U

* Value 14 days after castration.

($p > 0\ 1$) The testosterone excretion did not increase significantly in the 5 patients tested after HCG treatment (mean 3 3±1 8 μg per 24 hours)

The response to HCG stimulation has not been studied in normal controls. However in otherwise normal boys with ectopic or undescended testes this treatment has resulted in a significant increase in testosterone excretion and the procedure has been found useful to discriminate between cryptorchidism and testicular aplasia.

Employing our present bio-assay method which includes the use of 200 ml urine samples for extraction we have not observed detectable amounts of gonadotropin (FSH) in the urine of normal prepubertal children Two of the six intersex patients excreted considerable amounts of FSH (Table 3) In both these cases, histological examination of testicular tissue showed absence of spermatogenesis, whereas spermatogenesis was present in at least one testis in the other cases (Table 3) One patient (case 2) who had a base value of 11 I U FSH was given ethinylestradiol 0 05 mg b.i d for 4 days. FSH excretion on the 1st day of treatment was 1 I U and on the 4th day 2 I U

4 Genetic markers

Blood grouping and examination of Gm, Hp Gc, PGM and Pi types in the XX/XY mosaic patients and their parents did not reveal inconsistencies suggestive of chimerism in any of these patients.

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Diagnosis XX/XY mixed gonadal dysgenesis



Fig. 3 *Case 1* Full view of the patient at 11 years of age showing slight cubitus valgus and hypoplastic external genitalia.

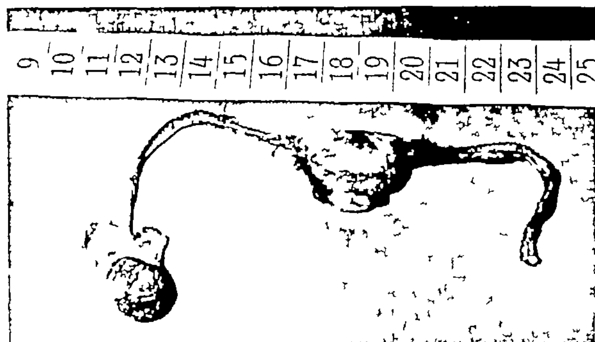


Fig 4 *Case 1* Gross operative specimen showing a normal infantile uterus, vas deferens with testis on the right, and Fallopian tube on the left No gonad was found on the left side

Fig 5 *Case 1* Section of intraabdominal gonad showing seminiferous tubules composed of Sertoli cells. There is no evidence of germ cells. Note intratubular calcification (H & E × 150)



Fig. 6 *Case 1* Section through tubular structure extending from left cornu. The histologic features are characteristic of the Fallopian tube (H & E × 60)

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Physical examination showed rather tall, bright and lert boy. His height was 125 cm (4 cm bove 97.5th percentile) corresponding to height age of 7 4/12 years. The weight was 22 kg (10th percentile). X-ray of both wrists showed difference in bone age of about 6 months whichever standard female or male was used. However when male standard was used on the right side and female on the left, both sides were equal with bone age of 3 years.

The penis was small measuring about 3 by 1.3 cm. As result of previous surgery the meatus had been brought onto the tip of the glans. Both testes were palpable in the scrotum and appeared normal on clinical examination. No vagina could be demonstrated on urethra-cystography.

Cytogenetic analyses m epeated cultures from peripheral blood and bone marrow showed 46,XX/46,XY mosaic (Table 1). The results of hormone analyses are listed in T bles 2 and 3.

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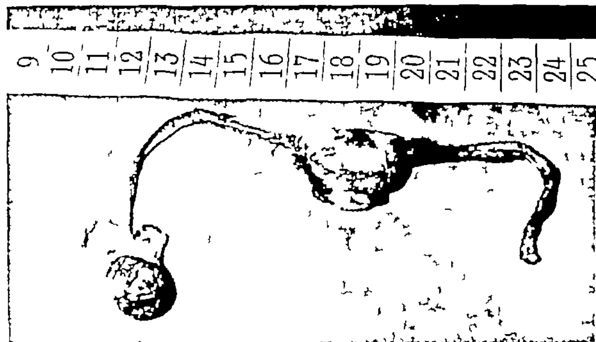


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Fig. 6. Case 1 Section through tubular structure extending from left cornu. The histologic features are characteristic of the Fallopian tube. (H & E ×60)

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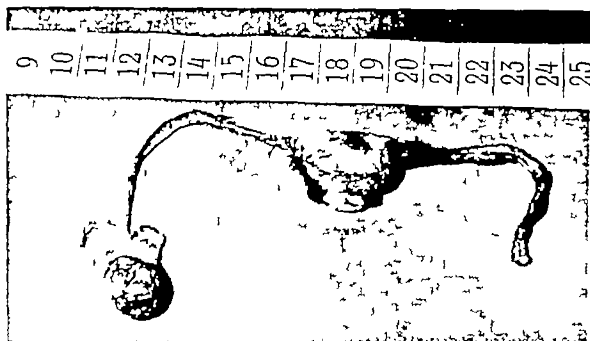


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Fig 7 *Case 2* Low-power photomicrograph of gonadal biopsy specimen. Both gonads showed essentially the same picture. The gonads were lined by an epithelium which in some areas was tall and columnar and in others tapered down to low cuboidal. Seminiferous tubules were absent. In centre a few tubules of probable mesonephric origin and an aggregation of cells. (H & E ×60)

ound nuclei with coarsely clumped chromatin Fig 8) Deeper in the "medulla a few aggregations of similar cells were seen (Fig 9) and they also seemed to reside in the covering *columnar epithelium* These cells, which were considered germ cells, were frequently observed in mitosis (Fig 9) A few tubules with a single layer of cuboidal epithelium were observed in some sections (Fig 7) These tubules were interpreted as tubules derived from the mesonephros.

No structure was found which allowed the identification of the biopsy specimens as gonadal tissue with certainty A tentative interpretation is that these gonads represent severely embryonic testes in which a cortical zone of coelomic epithelium has persisted. However unlike the undifferentiated embryonal testes there were no cord like structures in the medullary portion, and it is therefore necessary to postulate that these had disappeared, or failed to develop.

In spite of the lack of any histologic evidence of a testicular nature of these gonads, they evidently had the fetal competence to cause regression of the Mullerian ducts and to impose maleness, although incomplete on the external genitalia. From a functional point of view they might therefore be considered testes.

Diagnosis LV/VI *Male pseudohermaphroditism*

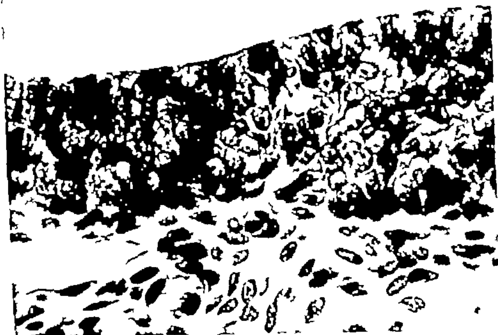


Fig. 8. Case 2. High-power photomicrograph of the tall columnar epithelium lining the surface of the gonads. Primitive germ cells reside in the epithelium and are evident as large cells with large nuclei with coarsely clumped chromatin. (H & E ×600)

Fig 9 Case 2. Detail of cellular aggregation in the medullary portion of th gonads. The primitive germ cells are intermingled with smaller cells with small round



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Diagnosis XX/XY Male pseudohermaphroditism.

Fig. 11 *Case 4* Cross section of rudimentary unicorn uterus. (H & E ×35)

Fig. 12. *Case 4* Cross section of Fallopian tube. (H & E ×35)

Case 3 This patient was a 7 year old boy He was the fourth child of a 32-year old mother and a 39-year old father The pregnancy was uneventful. A penoscrotal hypospadias with marked cordae had been noted at birth and he had had a two stage surgical repair

Clinical examination showed a healthy well-proportioned boy His height was 125 cm (50th percentile)and weight 26 kg (75th percentile) His bone age was in accordance with chronological age. The penis was well formed and measured 4.5 by 2 cm Both gonads were present in the scrotum and appeared normal on clinical examination. An urethracystography revealed no vaginal pouch

Buccal smears were sex chromatin negative. Chromosome studies were carried out on three different occasions in lymphocyte cultures from peripheral blood and once in cultures from bone marrow The results were consistent with a 46,XX/46 XY mosaicism (Table 1) The results of hormone analysis are listed in Tables 2 and 3

An exploratory laparotomy revealed absence of Müllerian remnants. Vasa deferentia were observed on both sides. Both gonads were exposed for biopsy They had the gross appearance of normal testes with epididymis and measured 2.0 by 1 2 cm Microscopic examination of biopsy specimens from both testes presented no abnormal features.

Diagnosis XX/XY *male pseudohermaphroditism.*

Case 4 This 9-year old boy was the first child of a 23-year old mother and a 32-year old father Both parents and 3 siblings were healthy and of normal stature. A two-stage operation for penoscrotal hypospadias was carried out between 2 and 4 years of age. The right testis had not descended. The motor and mental development had been normal and, based on clinical assessment and school achievements, his intelligence was considered normal

Physical examination revealed a rather stocky boy with a broad chest, somewhat broad and short neck cubitus valgus and genu varum (Fig 10) Epicantal folds, a high arched palate and multiple small, deeply pigmented nevi were also noted.

The height was 126 cm (10th–2.5th percentile) and weight 33,5 kg (4 kg above 97.5th percentile)

The penis was fairly well-formed and measured about 4 by 1.5 cm. No gonad could be palpated on the right side. The left side of the scrotum contained a gonad which ap-

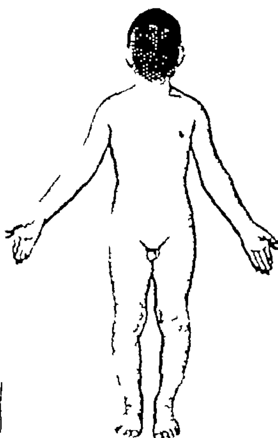


Fig 10 *Case 4* Patient 9 years old. Note features of the Turner phenotype.

peared to be a testis of normal prepubertal size. Bone age corresponded to chronological age. Intravenous pyelography revealed a horseshoe kidney No vagina was discovered on urethra cystography

Buccal smears were sex chromatin negative Chromosome analysis in cultured leucocytes from peripheral blood showed a 45 XO/46,XY mosaic. A total of 100 metaphases were examined. Twenty-one contained 45 chromosomes with a 45,XO karyotype and 79 had a normal male karyotype. The results of hormone analysis are depicted in Tables 2 and 3

Exploratory laparotomy disclosed an oval shaped gonad measuring about 2 cm in length by 1 cm in width, located on the right side of the pelvis in the position where one would expect to find the ovary In the midline between the bladder and rectum and extending slightly to the right, a small structure was seen which, on microscopic examination,

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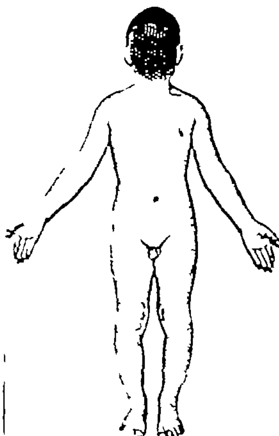


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Case 3 This patient was a 7 year old boy He was the fourth child of a 32 year old mother and a 39-year old father The pregnancy was uneventful. A penoscrotal hypospadias with marked cordae had been noted at birth and he had had a two stage surgical repair

Clinical examination showed a healthy well-proportioned boy His height was 125 cm (50th percentile)and weight 26 kg (75th percentile) His bone age was in accordance with chronological age The penis was well formed and measured 4.5 by 2 cm. Both gonads were present in the scrotum and appeared normal on clinical examination An urethracystography revealed no vaginal pouch

Buccal smears were sex chromatin negative. Chromosome studies were carried out on three different occasions in lymphocyte cultures from peripheral blood and once in cultures from bone marrow The results were consistent with a 46,XX/46,XY mosaicism (Table 1) The results of hormone analysis are listed in Tables 2 and 3

An exploratory laparotomy revealed absence of Müllerian remnants. Vasa deferentia were observed on both sides. Both gonads were exposed for biopsy They had the gross appearance of normal testes with epididymis and measured 2 0 by 1.2 cm. Microscopic examination of biopsy specimens from both testes presented no abnormal features.

Diagnosis XX/XY *male pseudohermaphroditism.*

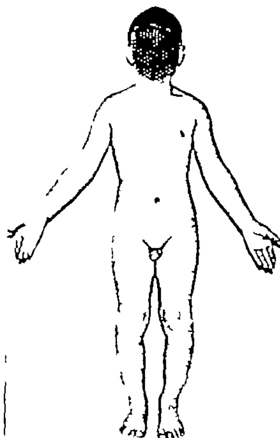


Fig 10 *Case 4* Patient 9 years old. Note features of the Turner phenotype

Case 4 This 9 year old boy was the first child of a 23-year old mother and a 32 year old father Both parents and 3 siblings were healthy and of normal stature A two-stage operation for penoscrotal hypospadias was carried out between 2 and 4 years of age. The right testis had not descended. The motor and mental development had been normal and, based on clinical assessment and school achievements his intelligence was considered normal

Physical examination revealed a rather stocky boy with a broad chest, somewhat broad and short neck, cubitus valgus and genu varum (Fig 10) Epicantal folds, a high arched palate and multiple, small deeply pigmented nevi were also noted.

The height was 126 cm (10th–2.5th per centile) and weight 33 5 kg (4 kg above 97.5th percentile)

The penis was fairly well formed and measured about 4 by 1.5 cm. No gonad could be palpated on the right side. The left side of the scrotum contained a gonad which appeared to be a testis of normal prepubertal size. Bone age corresponded to chronological age. Intravenous pyelography revealed a horseshoe kidney No vagina was discovered on urethracystography

Buccal smears were sex chromatin negative. Chromosome analysis in cultured leucocytes from peripheral blood showed a 45,XO/46,XY mosaic A total of 100 metaphases were examined. Twenty-one contained 45 chromosomes with a 45,XO karyotype and 79 had a normal male karyotype. The results of hormone analysis are depicted in Tables 2 and 3

Exploratory laparotomy disclosed an oval shaped gonad measuring about 2 cm in length by 1 cm in width located on the right side of the pelvis in the position where one would expect to find the ovary In the midline between the bladder and rectum and extending slightly to the right, a small structure was seen which on microscopic examination,

Fig 14 *Case 4* Multinucleated "neuter cells" (H & E × 600)

Fig. 15 *Case 4* "Neuter cells" showing incipient hyaline degeneration. (H & E × 600)

proved to be a rudimentary unicorn uterus (Fig 11) Arising from the cornu of this structure was an infantile fimbriated Fallopian tube ending nearby the gonad (Fig 12) A second structure which proved to be a vas deferens emerged from the right internal ring and led to the right side of the pelvis. The gonad, Fallopian tube, right vas deferens and the rudimentary uterus were removed

On microscopic examination the gonad had the features of a dysgenetic testicle. The medulla was composed of testicular tubuli which contained Sertoli cells and many round, fairly large germ cells with clear cytoplasm and prominent round nuclei of varying size (Fig 13 and 14) Some of these cells contained two or more nuclei Other cells showed degenerative changes with disintegration and hyalinization (Fig 15) Deeper in the medulla there were numerous tubules with a single layer of cuboidal epithelium. These tubules were interpreted as rete tubules or tubules derived from the mesonephros. Definite epididymal tissue was not identified. The histological examination of biopsy specimens from the left scrotal testicle showed the normal structure of an immature testis.

Diagnosis XO/XY male pseudohermaphroditism.

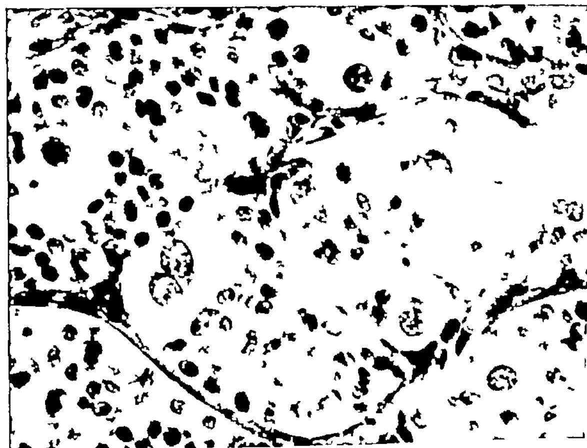


Fig 13 *Case 4* Section of right intraabdominal testis. The seminiferous tubules contained a large number of undifferentiated germ cells ("neuter cells") which are evident as large, round cells with clear cytoplasm and large, round nuclei. (H & E × 600)

Fig. 14. *Case 4.* Multinucleated "neuter cells" (H & E × 600)

Fig. 15. *Case 4.* "Neuter cells" showing incipient hyaline degeneration. (H & E × 600)

Case 5 This patient was a 1 9/12 year old boy He was the only child of a 21 year old mother and a 23-year old father The pregnancy had been uneventful The birth weight was 3710 g and length 49 cm. The motor and mental development was normal At the age of one year he had been operated for left-sided torsion of the testicle

Physical examination showed a healthy well proportioned boy No anomalies reminiscent of Turner's syndrome were noted The height was 83 cm (25th percentile) and weight 12 2 kg (50th percentile) Bone age corresponded to chronological age

Examination of the external genitalia showed a small penis in marked chordae and a scrotal hypospadias. The urinary meatus was located just posterior to the penoscrotal juncture. The scrotum was bifid and resembled fused labia majora (Fig 16) Testis-like structures were palpated on both sides of the scrotum but on the right it was impossible to make out the limits of either the epididymus or the testicle Urethracystography showed a vagina communicating with the posterior urethra (Fig 17)

Buccal smears were sex chromatin negative Chromosome analyses were carried out in cultures from peripheral blood and disclosed a 45 XO/46,XY mosaic Of thirty-five examined metaphases, 20 contained 45 chromosomes with an XO sex chromosome complement and the remaining 15 showed a normal male

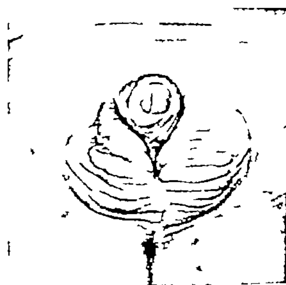


Fig 16. *Case 5.* Appearance of external genitalia after cordectomy Bifid scrotum with scrotal hypospadias.



Fig 17 *Case 5* Urethracystography revealed a vagina communicating with the posterior part of urethra

karyotype The results of hormone analyses are listed in Tables 2 and 3

An exploratory laparotomy revealed no Müllerian structures. The gonads were then exposed for biopsy Both gonads measured about 2 by 1 cm and on the left side the appearance was that of an infantile testis with epididymus. On the right side there was a peculiar coiled structure in the expected position of the epididymus. When uncoiled this structure assumed a form resembling that of a Fallopian tube with mesosalpinx to which the gonad was attached in an ovarian-like fashion (Fig 18) Within the 'mesosalpinx' was a somewhat firmer string of tissue which originally was thought to represent vas deferens. However multiple sections through the tube-like structure did not reveal any Mullerian derivatives and the microscopic appearance was that of a gubernaculum. Likewise the string thought to be vas deferens only contained connective tissue without any remnants of Wolfian elements. Sections through the mesosalpinx" opposite to the gubernaculum disclosed a Fallopian tube lined with immature tubular epithelium on one side of the section, and on the other side multiple ducts interpreted to be of mesonephric origin (Fig 19) The microscopic appearance of the gonad was that of a dysgenetic testicle with a cortical rudiment composed of a wavy stroma of connective tissue with scattered rudimentary tubules (Fig 20) and a medullary portion



Fig 18. Case 5. Gross operative specimen removed from the right side of the scrotal sac.



composed of immature seminiferous tubules. The tubules contained Sertoli cells and few spermatogonia and occasionally large germ cells with clear cytoplasm and prominent, round nuclei Some of these cells showed degenerative changes, and some tubules contained laminated concretions which seemed to represent the end point of this degeneration (Fig 21) In some locations the germ cells were surrounded by small Sertoli-like cells with oval nuclei arranged in single row along the periphery of the germ cell (Fig 22) Biopsy specimens from the other testicle showed an essentially identical picture.

Diagnosis XO/XY male pseudohermaphroditism.

Fig. 19. Case 5. Cross section of the mesosalpinx-like structure showing the general relation between the Fallopian tube and the mesonephric ducts. (H & E $\times$ 15)

Case 5 This patient was a 1 9/12 year old boy He was the only child of a 21 year old mother and a 23-year old father The pregnancy had been uneventful The birth weight was 3710 g and length 49 cm. The motor and mental development was normal. At the age of one year he had been operated for left-sided tor sion of the testicle.

Physical examination showed a healthy well proportioned boy No anomalies reminiscent of Turner's syndrome were noted. The height was 83 cm (25th percentile) and weight 12.2 kg (50th percentile) Bone age corresponded to chronological age

Examination of the external genitalia showed a small penis in marked chordae and a scrotal hypospadias The urinary meatus was located just posterior to the penoscrotal juncture The scrotum was bifid and resembled fused labia majora (Fig 16) Testis-like structures were palpated on both sides of the scrotum but on the right it was impossible to make out the limits of either the epididymus or the testicle Urethracystography showed a vagina communicating with the posterior urethra (*Fig* 17)

Buccal smears were sex chromatin negative. Chromosome analyses were carried out in cultures from peripheral blood and disclosed a 45,XO/46,XY mosaic Of thirty-five examined metaphases 20 contained 45 chromosomes with an XO sex chromosome complement and the remaining 15 showed a normal male

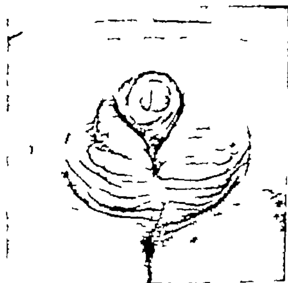


Fig 16 *Case 5* Appearance of external genitalia after cordectomy Bifid scrotum with scrotal hypospadias.



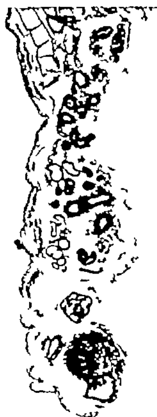
Fig 17 *Case 5* Urethracystography revealed a vagina communicating with the posterior part of urethra

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Fig 18. *Case 5* Gross operative specimen removed from the right side of the scrotal sac.



composed of immature seminiferous tubules. The tubules contained Sertoli cells and a few spermatogonia and occasionally large germ cells with clear cytoplasm and prominent, round nuclei. Some of these cells showed degenerative changes, and some tubules contained laminated concretions which seemed to represent the end point of this degeneration (Fig 21) In some locations the germ cells were surrounded by small Sertoli-like cells with oval nuclei arranged in single row along the periphery of the germ cell (Fig 22) Biopsy specimens from the other testicle showed an essentially identical picture

Diagnosis XO/XY male pseudohermaphroditism.

Fig. 19 Case 5 Cross section of the mesosalpinx-like structure showing the general relation between the Fallopian tube and the mesonephric ducts. (H & E x 15)

Fig 20 *Case 5* Section at the periphery of the removed testis showing wavy fibrous stroma resembling that of an ovary and rudimentary tubular structures. (H & E × 35)

Fig 21 *Case 5.* Seminiferous tubule from the right testis containing an i atubular body (H & E ×600)

Fig. 22. Case 5. Section of the right testis showing seminiferous tubule with germ cell ("neuter cell") surrounded in follicleloid pattern by single row of small cells with oval nuclei (Sertoli cells) (H & E ×600)

Case 6 This 12-year old boy was the sixth child of a 42-year old mother and 44-year old father The mother' height was 162 cm and the father's 167 cm. Two of the siblings were of verage stature and the other 3 of somewhat short statur like their parents H had shown normal motor and mental development and his school chievements were quite satisfactory He had had successful two-stage surgical repair for penoscrotal hypospadias The right testis had not descended.

Physical examination showed a healthy looking boy with android body build. H had slight cubitus valgus but otherwise there were no anomalies suggestive of Turner syndrome The height was 140 cm (10th–2.5th percentile) and weight 34 kg (75th percentile) Bone age corresponded to chronological age.

The penis was well-formed and measured about 4 by 2 cm. The right side of the scrotum was empty and hypoplastic. The left side contained clinically normal prepubertal testis (Fig 23)

Buccal smears were sex chromatin negative Chromosome analysis in repeated cultures from peripheral blood and in cultures from bone marrow all showed a normal male



Fig 23 Case 6. Appearance of external genitalia at 12 years of age after surgical repair of a penoscrotal hypospadias. Right-sided cryptorchidism with hemiscrotal hypoplasia. A right sided inguinal hernia sac contained a rudimentary uterus with Fallopian tube.

Fig 20 *Case 5* Section at the periphery of the removed testis showing wavy fibrous stroma resembling that of an ovary and rudimentary tubular structures. (H & E × 35)

Fig 21 *Case 5.* Seminiferous tubule from the right testis containing an intratubular body (H & E × 600)

Fig. 22. *Case 5.* Section of the right testis showing seminiferous tubule with germ cell ("neuter cell") surrounded in follbculoid pattern by single row of small cells with oval nuclei (Sertoli cells) (H & E ×600)

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Physical examination showed healthy looking boy with android body build. H had slight cubitus valgus but otherwise there were no anomalies suggestive of Turner syndrome. The height was 140 cm (10th–2.5th percentile) and weight 34 kg (75th percentile) Bone age corresponded to chronological age.

The penis was well-formed and measured about 4 by 2 cm. The right side of the scrotum was empty and hypoplastic. The left side contained clinically normal prepubertal testis (Fig 23)

Buccal smears were sex chromatin negative. Chromosome analysis in repeated cultures from peripheral blood and in cultures from bone marrow all showed normal male



Fig. 23. *Case 6* Appearance of external genitalia at 12 years of age, after surgical repair of a penoscrotal hypospadias. Right-sided cryptorchidism with hemiscrotal hypoplasia. A right-sided inguinal hernia sac contained rudimentary uterus with Fallopian tube.



Fig 24 *Case 6* Cross section of tube-like structure extending from a rudimentary uterus. Both Fallopian tube and Wolfian ducts are evident (H & E × 15)

karyotype (46 XY) The results of hormone analysis are depicted in Tables 2 and 3

An incision over the right inguinal canal revealed a hernia sac which contained a peculiar tube like structure attached to a mesentery The structure had a club-shaped end about 7 mm in diameter and tapered down to a small tube The tube measured 3–4 mm in diameter and about 4 cm in length and ended in a soft structure resembling the fimbriated end of a Fallopian tube Nothing suggesting vas deferens could be found On histologic examination, the club-shaped end had the features of a myometrium without epithelial elements. Sections through the tube-like structure revealed a Fallopian tube lined with columnar epithelium and in the tissue adjacent to the tube there were several Wolfian ducts with muscular coat (Fig 24) Gonadal tissue was not identified. Histologic examination of biopsy material from the left gonad showed the picture of a normal prepubertal testis with spermatogonia

Diagnosis XY mixed gonadal dysgenesis

Case 7 This patient was a girl who was first seen at the age of 2 9/12 years. She was the first child of healthy unrelated parents. The child was thought to be a cryptorchid, hypospadic boy and was referred for a first stage operation for hypospadias.

Her height was 103 cm (1 cm above 97 5th percentil) and the weight 15 1 kg (10th percentile) Height ge 4 years The bone age (Greulich and Pyle standard) corresponded to 9 years.

Clinical examination of external genitalia showed a funnel-shaped single orifice in the middle of a large phallus which measured 5 by 2 cm (Fig 25 and 26) The labio-scrotal folds were fused in the midline and no gonads could be palpated within the scrotal-lik tissue. A few sexual hairs were present t the base of the phallus. Buccal smears showed a sex chromatin positive pattern, and chromosome analysis revealed a normal female karyotype (46,XX)

A diagnosis of congenital virilizing adrenal hyperplasia was suspected and confirmed by



Fig 25. *Case 7* Female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia. Appearance of external genitalia at 2 9/12 years of age. Large phallus and beginning of sexual hair



Fig 26. *Case 7* External genitalia. View showing funnel-shaped urethral meatus in the middle of th phallus. Fused labio-scrotal folds give resemblance to an empty scrotum.

hormone analyses which showed elevated urinary excretion of 17-ketosteroids (7 4 mg per 24 hours) and pregnantriol (3 9 mg per 24 hours)

It was decided t change her sex of rearing t female. Following drenal suppression with cortisone therapy she had reconstructive surgery to bring the external genitalia in accordance with her sex of rearing

Diagnosis Female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia.



Fig 24 *Case 6* Cross section of tube-like structure extending from a rudimentary uterus. Both Fallopian tube and Wolfian ducts are evident. (H & E × 15)

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Diagnosis *YY mixed gonadal dysgenesis*

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A diagnosis of congenital virilizing adrenal hyperplasia was suspected, and confirmed by



Fig. 25. *Case 7* Female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia. Appearance of external genitalia at 2 9/12 years of age. Large phallus and beginning of sexual hair



Fig 26 *Case 7* External genitalia. View showing funnel-shaped urethral meatus in th middle of th phallus. Fused labio-scrotal folds give resemblance t an empty scrotum.

hormone analyses which showed elevated urinary excretion of 17 ketosteroids (7 4 mg per 24 hours) and pregnantriol (3.9 mg per 24 hours)

It was decided to change her sex of rearing to female. Following adrenal suppression with cortisone therapy she had reconstructive surgery to bring the external genitalia in accordance with her sex of rearing.

Diagnosis Female pseudohermaphroditism due to congenital rilizing adrenal hyperplasia.

Discussion

1 Etiology of hypospadias

Hypospadias is a fairly common anomaly of the urogenital system Different surveys have shown a rather wide variation in the estimated frequency ranging from 0.55 per 1 000 to 6.25 per 1 000 (21) In a study of a large series of newborn in Denmark, Sorensen found a frequency of 3 26 per 1 000 (108) The glandular type is by far the most common form and in a population this type probably accounts for about three-quarters of the cases. Among the remaining cases the frequency of the penile form is probably about equal to the combined frequency of the penoscrotal and the scrotal form (108)

The etiology of hypospadias has been obscure Sorensen found familial occurrence in 28 per cent of cases and a concordance rate in twins of about 50 per cent He concluded that the abnormality was transmitted as a recessive trait with irregular manifestation (108) Reifenstein s syndrome constitutes a special form of hereditary hypospadias. The condition is transmitted either as an X linked recessive trait or a sex linked autosomal dominant It is characterized by hypospadias, postpubertal testicular atrophy and usually gynecomastia (17) Hypospadias of various degrees may present as part of multiple congenital malformations, and in some instances the constellation of malformations is sufficiently characteristic to be diagnostic of a recognized syndrome (13 82 102) Hypospadias may also be part of multiple congenital anomalies seen in different autosomal chromosome abnormalities (2 66) These observations indicate that the anomaly may sometimes be the result of more or less unspecific noxious conditions affecting the developmental process of the early primordium of the external genitalia

In the present material sex chromosome mosaicism was present in 5 of 80 patients studied This result is at variance with that obtained by Juberg et al (62) They studied a smaller series of 21 patients including 8 glandular cases, and found no case with sex chromosome abnormality However 14 of their patients had one or more malformations in addition to hypospadias, and their material is therefore probably not comparable to that in the present study which excludes patients with multiple anomalies.

Conceivably an abnormal sex chromosome constitution will interfere with the normal development and function of the fetal testes resulting in incomplete masculinization and hypospadias Anticipating later more detailed considerations a fair amount of circumstantial evidence indicates that maternal progestin treatment in early pregnancy might also interfere with fetal testicular function and thereby be the cause of hypospadias Thus, by means of the relatively simple methods employed in this study an etiological factor which presumably might lead to impairment in fetal testicular function has been uncovered in 10 out of 79 male hypospadic patients studied In addition one patient with normal male karyotype showed evidence of impaired

function of the fetal testes by the presence of Mullerian remnants. Thus, a pathogenetic mechanism which could conceivably operate through a reduction of fetal testicular function has been unveiled in 11 patients, or in 14 per cent of cases.

In the present material the distribution of patients with regard to the site of the urethral orifice is not representative since the more severe forms are over-represented. However the distribution of different types within the more severe forms seems to be fairly representative For this reason, and because the glandular portion of the urethra has a particular embryogenesis, it might be justified to disregard glandular hypospadias and only consider the more severe forms. It then appears that some evidence of impairment in fetal testicular function has been unveiled in 11 out of 48 patients, or in 21 per cent of cases of this category

2. Differentiation of the external genitalia and the role of maternal progestin treatment

At an early stage in embryonal development the external genitalia are constituted by a urogenital groove which is limited by two urethral folds, and, more laterally by the labioscrotal swellings The urogenital sinus opens into the urethral groove by the primitive urogenital ostium. Anterior to the urogenital sinus is the genital tubercle which either may remain small as the clitoris or develop into the corpora cavernosa and glans of the penis. The urethral folds may remain separate in which case they constitute the labia minora, or they may fuse to form a corpus spongiosum enclosing a phallic urethra. The labioscrotal swellings may remain separate to form labia majora, or they may shift caudally and fuse in the midline to form scrotum and the ventral epidermal covering of the penis.

In males, the urethral groove fuses first in the pelvic region, progressively bringing the urogenital ostium onto the phallus. These changes become recognizable at about 8 weeks of gestation and by the fourteenth week the urethra has closed as far as the glans (49 58) The urethra is then continued along the urethral plate which represents a solid part of the urethral primordium, to the tip of the genital tubercle. By splitting, the plate is first converted into a trough which subsequently recloses into a tube that continues as urethra to its permanent opening If the urethral groove fails to fuse anywhere along its extent, hypospadias proximal to the glans results. Glandular hypospadias appears to result from failure of the union of the split urethral plate.

As already alluded to there is an inherent tendency for the external genitalia to feminize and differentiation along male lines will occur only if maleness is imposed by the fetal testes. This masculinization is probably brought about by testosterone and/or other androgenic hormones from the fetal testis. The fetal testicular Leydig cells begin to proliferate at about the eighth fetal week and the maximum number of fully differentiated cells is reached at about the twelfth week (79) This sequence of events coincides with the characteristic course of chorionic gonadotropin production which starts by the fourth week of pregnancy and reaches a peak by the eighth to twelfth week, and it seems likely that the development of the fetal Leydig cells is initiated by chorionic gonadotropin. Histochemical studies have shown that the activity of 3β-hydroxy steroid dehydrogenase appears in the Leydig cells before any other tissue within the fetus of either sex (37) Activity of this microsomal enzyme is essential for the conversion of 3β-alcohols to the corresponding 3β-ketones in the early biosynthetic pathway of nearly every biologically active steroid hormone. It has been shown that the peak activity of this enzyme coincides with the peak chorionic gonadotropin production and maximum Leydig cell proliferation (6 79) and all these phenomena coincide with the time of urethral groove fusion in the male fetus. It has also been demonstrated that fetal testes are able to synthesize testosterone *in vitro* from labelled precursors (3)

Discussion

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2 Differentiation of the external genitalia and the role of maternal progestin treatment

At an early stage in embryonal development the external genitalia are constituted by a urogenital groove which is limited by two urethral folds, and more laterally by the labioscrotal swellings The urogenital sinus opens to the urethral groove by the primitive urogenital ostium. Anterior to the urogenital sinus is the genital tubercle which either may remain small as the clitoris or develop into the corpora cavernosa and glans of the penis. The urethral folds may remain separate, in which case they constitute the labia minora, or they may fuse to form a corpus spongiosum enclosing a phallic urethra. The labioscrotal swellings may remain separate to form labia majora, or they may shift caudally and fuse in the midline to form scrotum and the ventral epidermal covering of the penis.

In males, the urethral groove fuses first in the pelvic region, progressively bringing the urogenital ostium out the phallus. These changes become recognizable at about 8 weeks of gestation and by the fourteenth week the urethra has closed as far as the glans (49 58) The urethra is then continued along the urethral plate, which represents a solid part of the urethral primordium, to the tip of the genital tubercle. By splitting the plate is first converted into a trough which subsequently recloses into a tube that continues as urethra to its permanent opening If the urethral groove fails to fuse anywhere along its extent, hypospadias proximal to the glans results. Glandular hypospadias appears to result from failure of the union of the split urethral plate.

As already alluded to there is an inherent tendency for the external genitalia to feminize and differentiation along male lines will occur only if maleness is imposed by the fetal testes. This masculinization is probably brought about by testosterone and/or other androgenic hormones from the fetal testis. The fetal testicular Leydig cells begin to proliferate at about the eighth fetal week and the maximum number of fully differentiated cells is reached at about the twelfth week (79) This sequence of events coincides with the characteristic course of chorionic gonadotropin production which starts by the fourth week of pregnancy and reaches a peak by the eighth to twelfth week, and it seems likely that the development of the fetal Leydig cells is initiated by chorionic gonadotropin. Histochemical studies have shown that the activity of 3β-hydroxysteroid dehydrogenase appears in the Leydig cells before any other tissue within the fetus of either sex (37) Activity of this microsomal enzyme is essential for the conversion of 3β-alcohols to the corresponding 3β-ketones in the early biosynthetic pathway of nearly every biologically active steroid hormone. It has been shown that the peak activity of this enzyme coincides with the peak chorionic gonadotropin production and maximum Leydig cell proliferation (6 79) and all these phenomena coincide with the time of urethral groove fusion in the male fetus. It has also been demonstrated that fetal testes are able to synthesize testosterone *in vitro* from labelled precursors (3)

If female embryos are exposed to androgenic stimulation in early fetal life their external genitalia can exhibit any degree of masculinization ranging from simple clitoral hypertrophy to the for mation of a penis with a complete phallic urethra (88 116) Normally the fetal adrenal does not seem to play a signif icant role in sex differentiation. However in female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia, the masculinization of the external genitalia is caused by androgens produced prenatally by the pathologic adrenal Female infants with congenital virilizing adrenal hyperplasia may be readily mistaken for hypospadic males or even a normal male infant with cryptorchism (88 116) This situation is well illustrated by case 7 in the present report.

Embryonic masculinization of the ex ternal genitalia of the female fetus has been frequently observed following ma ternal ingestion of testosterone or one of its known androgenic analogs during the first trimester of pregnancy (40) Under normal conditions the hormones cir culating in the mother do not disturb the sexual organogenesis of the fetus. This situation changes completely if synthetic oral progestins are administered Since progesterone itself is only very slightly active when given orally various syn thetic derivatives which may be taken by mouth have been widely used in pregnant women with habitual or threat ened abortion In 1942 Courrier and Jost reported that ethisterone a well known example of these synthetic steroids when administered to castrated pregnant rabbits had three effects a progestinal action with maintainance of gestation a masculinizing effect on the female fetus, and a slight feminizing effect on the male fetus (24) They warned against the use of such substances in the pregnant women That this warning was appropriate was amply demonstrated some 15 years later when the first reports of masculinization of the female infants due to maternal progestin treatment appeared (117) By 1960 Wilkins was able to collect 70 such cases and norethidrone and various commercial forms of ethisterone were responsible for most cases (118)

The virilizing effect of progestins on the female fetus has been confirmed by several investigators in experimental embryology whereas there is scanty information on a possible feminizing effect on the male fetus Junkmann and Neumann observed that relatively high doses of progesterone or of 19-nor 17α hydroxy progesterone might interfere with urethral groove fusion in a low percentage of fetal male rats (63) The same authors also studied a group of recently synthesized progestinal steroids differing slightly from hydroxyprogesterone and found that low doses of these steroids produced strikingly severe hypospadias in the major ity of male rat fetuses (63)

The apparently paradoxical effect of progestins on the sexual organogenesis of the male and female fetus is analogous to that observed in infants borne with a severe form of congenital virilizing adrenal hyperplasia due to genetic deficiency of 3β-hydroxysteroid dehydrogenase (15 35) Genetic male infants with this disorder have incomplete masculine development with hypospadias, whereas genetic females are born moderately virilized with clitorial hypertrophy but without displacement of the urethral orifice The explanation for this paradoxical effect is that impaired activity of 3β-hydroxy steroid dehydrogenase in the fetal testis leads to deficient production of testosterone or testosterone like steroids and thereby impaired masculinization. The response to 3β-hydroxysteroid dehydrogenase deficiency in the adrenals would be increased production of dehydroepiandrosterone which has androgenic effect sufficient to virilize the female fetus but insufficient to secure complete masculinization of the male fetus in the absence of testosterone. Reasoning along this line Goldman and Bongiovanni put forward the hypothesis that different progestins might have a common teratogenic action mimicking congenital adrenal hyperplasia with deficient 3β-hydroxysteroid dehy

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The information obtained in these experimental studies and the observations in the present study suggest that there might be a causal relationship between maternal progestin treatment in early pregnancy and development of hypospadias. This suggestion is also borne out by the relationship between th gestational age of the fetus at the beginning of progestin treatment and the position of the urethral meatus in the hypospadic infant This would imply that each section of the urethral groove might pass through a critical stage of masculinization which is probably reflected by this relationship (Fig 1) It could be argued that two of the mothers received treatment corresponding to an embryonic stage prior to that when the urethral groove fusion become recognizable. However it is not known when the urethral folds are conditioned for fusion, and information on individual variation in the process of fusion is completely lacking

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Although it cannot be claimed that there is a definite relationship between the occurrence of hypospadias and maternal progestin treatment, there is circum stantial evidence for suspicion of such a relation and such suspicion should exhort to caution in giving such drugs to pregnant women The beneficial effect of progestins in the threatened pregnancy has been questioned (5 100) With the simple laboratory methods now at hand to test for pregnancy there is no need for these potent steroids to be used for this purpose.

3. Gonadal sex differentiation and the role of the Y chromosome

Until the fifth to sixth week of embryonic life the development of the gonadal primordium proceeds in an identical fashion regardless of genetic sex. The gonadal primordium first appears as bilateral longitudinal thickenings of the coelomic epithelium overlying the mesonephros just lateral to the base of the dorsal mesentery (Fig 27) This constitutes the genital ridge and as mesonephros projects into the coelomic cavity it also raises the progressively swelling

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THE GONADOGENESIS

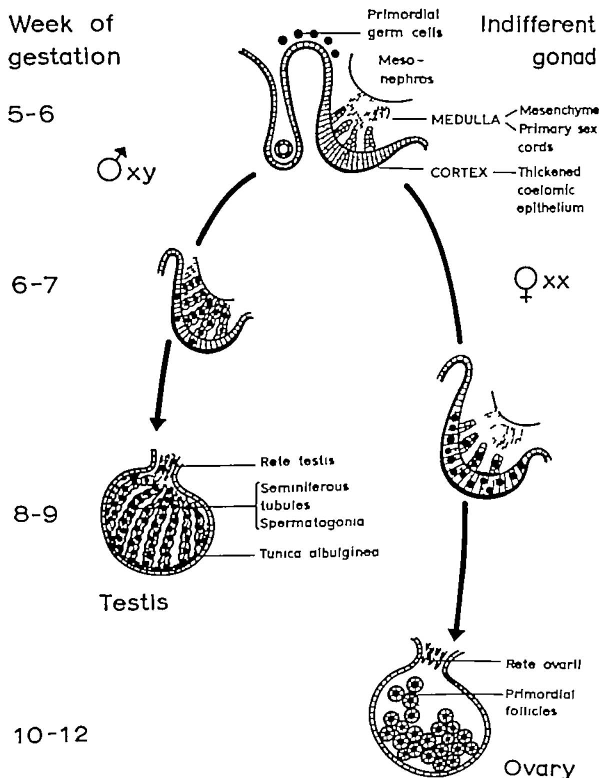


Fig 27 Human embryos of 5–6 weeks gestation have indifferent gonads. Primordial germ cells migrate into the gonad and seed in cortex and medulla. Testicular differentiation starts at 6–7 weeks gestation and is characterized by medullary development and regression of the cortex. Ovarian differentiation occurs later and is characterized by continuing proliferation of the cortical coelomic epithelium and regression of the medulla.

genital ridge. There is now considerable evidence that the germ cells do not originate in situ but migrate from the dorsal endoderm of the yolk sac through the hind gut wall and then through the dorsal mesentery to the primordial gonad (68, 122) The undifferentiated gonad can be divided into an outer cortex and an inner medulla, which are separated by a primary tunica albuginea (Fig 27) The cortex consists of the thickened coelomic epithelium and has the potentiality to develop into an ovary The medullary portion, which has the potentiality to differentiate to a testis, is composed of a mesenchymal stroma with condensed sheets of epithelial cells, or the so-called primary sex cords. Th majority of the primitive germ cells settle in the cortex. If the primitive gonad is destined to form a testis, the primary sex cords undergo marked proliferation about the seventh fetal week, and the germ cells are carried into the developing seminiferous tubules by ingrowths of the coelomic epithelium (Fig 27) During the same period the cortex slowly degenerates. Differentiation of th indifferent gonad into an ovary occurs about 2 weeks later than does testicular differentiation (96) The main features of ovarian development are the persistence and proliferation of the cortex (Fig 27) Whereas viable germ cells seem necessary for ovarian differentiation this may not be true for testicular differentiation (43 44)

Presumably the Y chromosome carries genetic material which is normally responsibl for testicular differentiation and information gained from patients with structurally abnormal Y chromosomes suggests that these genes are located on the short arm of the Y chromosome and close to the centromere (46) In general, the experience in patients with sex chromosome aberrations has been in accordance with these assumptions since testicular tissue occurs only when a normal Y chromosome is present in at least a portion of somatic cells. True hermaphrodites with XX sex chromosome complement and the so-called XX male syndrome are important exceptions to this general rule. These seemingly paradoxical cases may be explained by undiscovered mosaicism with a cell clone containing a Y chromosome or by the loss of cell clones carrying a Y chromosome after the critical period of gonadal differentiation In this connection it should be stressed that the cytogenetic findings in other tissues are by no means representative for the conditions in the gonads, and even when gonadal tissue is examined the Y containing clone might sometimes be difficult to unveil (18) An alternative explanation proposed by Ferguson-Smith, is exchange of sex determining genes between X and Y chromosomes during spermatogenesis (27) This hypothesis has recently gained considerable support from studies on the distribution of Xg groups in XX males and their families (89)

If it is accepted that the Y chromosome carries testis determining genes, *it still* remains unknown how these genes initiate and maintain testicular morphogenesis, and how the fetal testis achieves embryonic competence to impose maleness on the bivalent gonaducts and the un differentiated external genitalia. It appears that normal male sex differentiation requires at least three male determining genes one which initiates and maintains testicular morphogenesis one which causes the elaboration of the testicular substances responsible for the regression of the Mullerian ducts and finally one which is responsible for the production of the substances which impose maleness on the Wolfian ducts and external genitalia. Data obtained in experimental embryology and clinical experience in intersex conditions have accumulated a fair amount of evidence supporting the existence of the two latter substances (60) However the mechanism of action of the sex genes in bringing about ovarian or testicular organogenesis is still unsolved. In Witschi's classical concept the undifferentiated gonadal anlage produced two antagonistic inductors (121) In the female a gene F stimulates the cortex to produce cortexin" which inhibits the

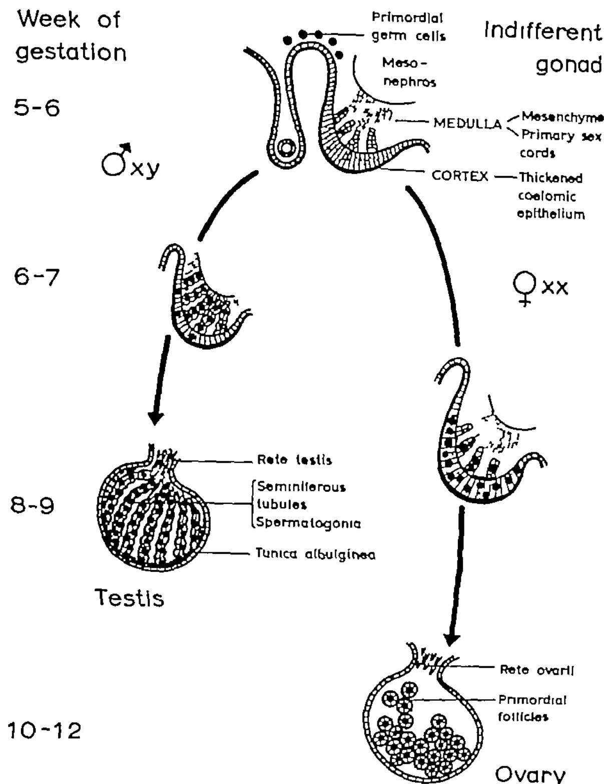


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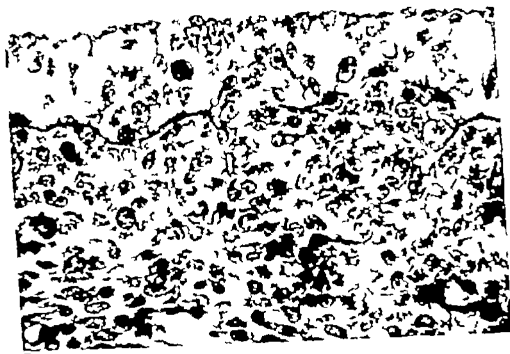




Fig 28 (Top) Section through persisting coelomic epithelium of the fetal ovary of a 48-day old bovine freemartin (Courtesy of Prof. A. Jost, Laboratoire de Physiologie Compa ée Université de Paris) Freemartins in cattle are heifers which have been masculinized under the influence of their bull co-twin, as consequence of early anastomosis between the placental circulations.

(Below) Section through the covering epithelium of the testes of case 5. Note the resemblance to the persisting coelomic epithelium of the freemartin fetus. (H & E ×600)

medulla and controls oogenesis, and in the male a gene M stimulates the medulla to produce medullarin which inhibits the cortex and stimulates spermatogenesis According to Jost many observations could as well be explained by assuming only one inductor or mechanism which imposes testicular organogenesis on a primordium which otherwise slowly becomes an ovary (59 61)

4 Gonadal histology and function in male pseudohermaphroditism

Most instances of gonadal dysgenesis occur in individuals with abnormalities in the sex chromosome complement The gonadal expression of a given sex chromosome abnormality however has shown rather wide variations Thus both in XO/XY and XX/XY mosaicism the range of variation has extended from bilateral streak gonads, through bisexual formations with both ovarian and testicular tissue to various degrees of testicular dysgenesis (Fig 31 and Table 4) Some of the morphological findings in testicular dysgenesis are probably best interpreted as the result of an arrest in embryological development. Bergada and coworkers described two patients who had ambiguous external genitalia remnants of Müllerian structures and a rudimentary testis on one side and vas deferens and a fairly normal testis on the opposite side. Histological examination of the rudimentary testes showed that the major portion of the gonads were composed of fibroblasts and undifferentiated cells resembling the mesenchymal cells of an embryonic gonad (10) In addition there were cells which were considered germinal cells, and in some locations these cells assumed a cord like structure suggesting slightly an embryonic gonad just before sex can be recognized However unlike an undifferentiated embryonic gonad and unlike that observed in case 2 of the present report, no cortical zone of coelomic epithelium could be recognized To my knowledge persistence of such epithelium in presumable testes has not been described previously In Figure 28 the epithelium covering the testes of the patient has been compared to the persisting coelomic epithelium of the fetal ovary of a 48-day old freemartin. (The freemartin condition is seen in cattle when there has been anastomosis between the placental circulation of embryos of dissimilar sex early in embryonic life. A significant feature of the freemartin heifer is that the external genitalia are usually female in type whereas the internal genitalia show varying degrees of masculinization In extreme cases the gonads may assume the appearance of testes and descend through the inguinal canals) The similarity of the covering epithelium of these gonads is rather striking However at this stage of embryonal development, the medulla adjacent to the coelomic epithelium of both prospective ovaries and testes is considerably more cellular than that found in the biopsy specimens from the patient (61 96) It is therefore necessary to postulate that the medullary portion or the primary sex cords, had regressed or failed to develop If Jost's postulate on one gonadal inductor which imposes maleness on the undifferentiated gonad is adopted (59 61) there is only a quantitative difference between the histological findings in the testes described by Bergada and his associates and that found in our case. The findings could then be explained by assuming that the production of male inductor at a critical stage in gonadal differentiation was insufficient to impose testicular morphogenesis but sufficient to prevent the gonads from becoming ovaries. In both cases described by Bergada and coworkers the embryonic testes were also deficient in producing the substances causing regression of the Müllerian ducts, whereas this competence was preserved by the morphologically more embryonic testes in our case. The latter observation suggests that there is a dichotomy between these two hypothetical substances

The cortical elements in these embryonic gonads should be distinguished from the so-called cortical rudiments in

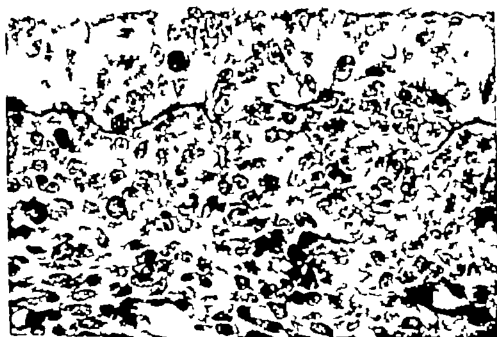




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dysgenetic testes. These rudiments consist of areas of ovarian like stroma, usually situated in the peripheral portion of the gonad and contain nests of cells believed to be of cortical origin (119) Such findings have now and then been observed in male pseudohermaphroditism and were also a feature of the testicular histology in case 5 of the present report (Fig 20) Bergada and his associates studied 19 patients with male pseudohermaphroditism with ambiguous or masculine external genitalia (10) The testes of most of these patients presented no characteristic or abnormal features. Cortical rudiments were present in 4 cases and in distinction to the rest of the group these patients all had Müllerian duct development with uterus and tubes.

The finding of large "germ" cells with clear cytoplasm and a prominent nucleus within the testicular tubules, like that particularly noted in case 4 (Fig 13 and 14) and to a lesser extent in case 5 has been interpreted as histologic evidence of *testicular dysgenesis (71)* These cells have been labelled "neuter cells" because it is believed that they lack the capacity to differentiate into functioning germ cells (71) Instead they seem to be displaced into the tubular lumen where they undergo degenerative changes with hyalinization of the cytoplasm and disintegration of the nucleus, and ultimately end up as laminated concretions (Fig 22 and 29) These concretions have been termed testicular intratubular bodies or intratubular pseudoovocytes. The latter term conno-

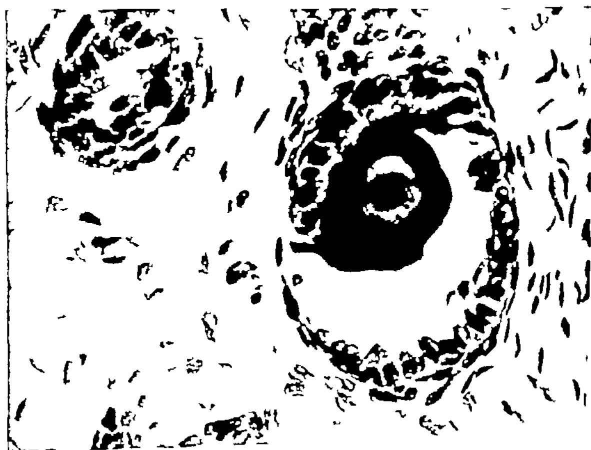


Fig 29 Testicular intratubular body An obvious nucleus is present in the centre It appears that the concretion occurs about an intact cell. (H & E × 600)
Section from testis of a 2 year old, mentally retarded boy with 45,XO/46 XY/46,XX/47,XXY mosaicism, intraabdominally located, rudimentary testes, hypoplastic mal external genitalia and absence of *Mullerian structures*. (Unpublished observati n)

tates their resemblance to ovocytes, and it has also been proposed that these bodies represent ovocytes (19) This view has been challenged by Bieger and coworkers who conclude that the bodies have their origin in displaced spermatogonia (11) Intratubular bodies have most frequently been observed in intersex conditions (10 11 19 112) but have also been noted in biopsy material from cryptorchid testes of prepubertal boys (11) Teter and Boczkowski found intratubular bodies in 14 patients with various intersex conditions associated with testicular dysgenesis (112) These authors believe that intratubular bodies signify the persistence of bisexual gonadal elements and that they are histological evidence of testicular dysgenesis Furthermore they believe that their presence indicates that the gonad has a predisposition to malignant transformation. It is believed that the gonadoblastomas arise from clusters of "neuter cells" and this neoplastic transformation is usually accompanied by varying degrees of degeneration and accumulation of intratubular concretions (71) There might also be a transitional zone between the gonadoblastoma and the adjacent testicular tissue with a histological picture resembling that found in the intraabdominal testis of case 4 in the present report (56, 113)

In most instances of intersex conditions associated with sex chromosome aberrations the histological findings in testicular tissue have been less conspicuous than those henceforth mentioned. However absence of spermatogenesis has been a frequent finding especially when the testes have been located intraabdominally (12 47 53) The histological picture is then characterised by tubules containing only Sertoli cells and frequently accompanied by some hyalinization of the basement membrane. Degenerative changes with calcification might also be seen as found in case 1 of the present report (Fig. 5)

In one of the XX/XY mosaic patients (case 3) the testicular structure were considered not to deviate from that found in prepubertal boys. Both testes were located in the scrotum and no Müllerian remnants were found. Thus these testes apparently had had the competence to cause regression of the Müllerian ducts during fetal life However the presence of hypospadias implies that the secretion of testosterone or testosterone like substances by the fetal testes had been insufficient to secure full masculinization of the external genitalia. The finding that the urinary testosterone excretion did not increase following gonadotropin administration suggests that a relative deficiency in the capacity to secrete testosterone might persist postnatally

The literature contains only scanty data on testicular function in children with abnormal sexual differentiation Saez and Bertrand measured plasma testosterone before and after stimulation with HCG in 8 children with unspecified forms of male pseudohermaphroditism (92) In 6 normal control children they found a mean value of plasma testosterone of 21 ± 6.5 ng/100 ml, and they observed a 25-fold increase following HCG stimulation. In the 8 male pseudohermaphrodites the mean basal value was 37 ± 12 ng/100 ml which was not significantly different from that found in the normal controls. However in 2 of the 8 patients the concentration of plasma testosterone following HCG stimulation was abnormally low The findings in these two children were rather analogous to the urinary testosterone findings in 5 of the patients in the present report who all showed normal basal values but failed to respond to HCG stimulation (Table 2) This failure to respond to a challenge is suggestive of a relative reduction in the testicular capacity to secrete testosterone.

Deficient endocrine function of the testes is also a possible explanation for the elevated urinary FSH excretion in 2 of the 6 children with intersex conditions (Table 3) since the increased FSH secretion might be the result of an inability of the testes, as the target organ, to accomplish negative feedback control

dysgenetic testes These rudiments consist of areas of ovarian like stroma usually situated in the peripheral portion of the gonad and contain nests of cells believed to be of cortical origin (119) Such findings have now and then been observed in male pseudohermaphroditism and were also a feature of the testicular histology in case 5 of the present report (Fig 20) Bergada and his associates studied 19 patients with male pseudohermaphroditism with ambiguous or masculine external genitalia (10) The testes of most of these patients presented no characteristic or abnormal features Cortical rudiments were present in 4 cases and in distinction to the rest of the group these patients all had Müllerian duct development with uterus and tubes

The finding of large germ cells with clear cytoplasm and a prominent nucleus within the testicular tubules like that particularly noted in case 4 (Fig 13 and 14) and to a lesser extent in case 5 has been interpreted as histologic evidence of testicular dysgenesis (71) These cells have been labelled neuter cells because it is believed that they lack the capacity to differentiate into functioning germ cells (71) Instead they seem to be displaced into the tubular lumen where they undergo degenerative changes with hyaliniza tion of the cytoplasm and disintegration of the nucleus and ultimately end up as laminated concretions (Fig 22 and 29) These concretions have been termed testicular intratubular bodies or intratubular pseudoovocytes The latter term conno-



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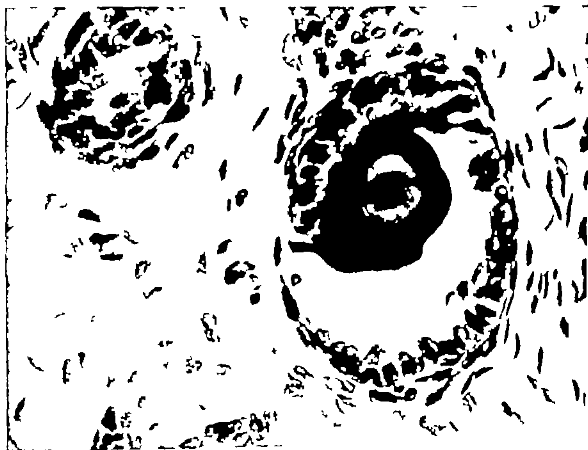


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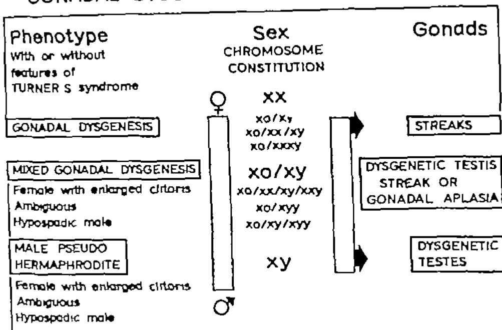


Fig 31 Range of phenotypic and gonadal expression in gonadal dysgenesis and its variants, and their relationship to the sex chromosome complement.

dysgenesis with a testis on one side and a streak or absent gonad on the other or *male pseudohermaphroditism* with bilateral testes. All three groups of patients might present with or without the somatic features of Turner's syndrome.

Sohval first pointed out the homogeneity of the second group of patients and proposed the designation mixed gonadal dysgenesis (103) Describing the same entity Bergada and coworkers used the term *asymmetrical gonadal differentiation* to emphasize the asymmetrical disparity of development which characterizes the condition (10) However the term mixed gonadal dysgenesis seems to have gained most adherents. Although most patients with mixed gonadal dysgenesis have had an XO/XY mosaic (12) this clinical entity is by no means confined to this chromosome aberration. The clinical findings in both case 1 and case 6 in the present report are in accordance with the concept of mixed gonadal dysgenesis and the sex chromosome constitution in these two cases was XX/XY and XY respectively Mixed gonadal dysgenesis associated with XX/XY mosaicism has been reported previously in two patients (25 83) and the clinical findings in these two cases have been summarized in Table 4 It is noteworthy that all three patients, so far reported with mixed gonadal dysgenesis and XX/XY mosaic, had no gonad opposite to the testis. In contrast, in *40 cases of XO/XY mosaicism* and mixed gonadal dysgenesis known to the author absence of the contralateral gonad was noted in only 5 cases (12 53 67 74) whereas it was represented by a streak gonad in the others. An XY karyotype has been reported in at least 8 other cases (4 42 53 63 87 112 123) In most of *these instances* chromosome analysis has only been carried out in one tissue and mosaicism might therefore have been missed. But in the absence of direct evidence of mosaicism, the possibility re

on the pituitary gland This brings up the controversial question of FSH regulation in the male. Figure 30 shows a diagram of the pituitary gonadal axis in the male It is generally agreed that the luteinizing hormone (LH) stimulates the Leydig cells to mature and secrete testosterone and that testosterone decreases LH secretion by a negative feed back mechanism (84 86) The inner circuit on the diagram is less well understood Under normal circumstances FSH possibly assisted by testosterone acts on the germinal cells to promote full spermatogenesis (84) However the substrate for the feed back link is unknown It has been postulated that the germ cells secrete a hypothetical substance which has been called "inhibin"

PITUITARY- GONADAL AXIS

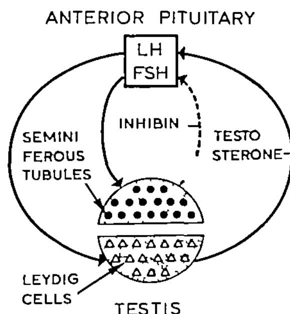


Fig 30 The luteinizing hormone (LH) stimulates the Leydig cells to mature and secrete testosterone and LH secretion is suppressed by the circulating testosterone The follicle stimulating hormone (FSH) acts on the seminiferous tubules to induce and maintain normal spermatogenesis. FSH secretion is thought to be suppressed by inhibin" a postulated substance secreted by germinal cells.

Damage to the germ cells will decrease inhibin" levels which in return would stimulate the anterior pituitary to increase FSH levels (51 84) The findings in the two patients in the present report might lend some support to the suggestion that spermatogenesis, or a factor related to spermatogenesis might be involved in the regulation of FSH However more data are needed and studies on the pituitary-gonadal axis in prepubertal children with various forms of testicular dysgenesis might be of particular interest. Recent development of sensitive immuno-assay methods for FSH and LH in plasma and urine renders such studies both feasible and challenging When combined with examination of testicular histology such assays might shed some light on the possible role of spermatogenesis in the pituitary-testicular relationship

5 Origin of XO/XY and XX/XY sex chromosome constitution and their gonadal and phenotypic expression

XO/XY mosaicism

The origin of an XO/XY mosaic is best explained by the loss of a Y chromosome during an early mitotic division of an XY zygote.

There is no single typical clinical picture in individuals with XO/XY mosaicism. The phenotypes range from an almost normal female with streak gonads to an almost normal male with one undescended testicle However the reported cases of XO/XY mosaicism have usually had either some type of gonadal dysgenesis or some type of male pseudohermaphroditism (75 77) and this spectrum of phenotypes in this particular chromosome aberration explains the long recognized overlapping between the syndrome of gonadal dysgenesis and male pseudohermaphroditism (Fig 31) As indicated in the figure the gonadal and corresponding phenotypic expression in most patients with XO/XY mosaic fall into one of three groups *gonadal dysgenesis* with streak gonads *mixed gonadal*

that these mosaic patients should be distinguished from the so-called "male Turner's syndrome" a term which has been linked to a heterogenous group of genotypic and phenotypic males with short stature, webbed neck, hypogonadism, mental retardation and frequently congenital pulmonary stenosis (29 80 81)

XX/XY mosaicism

Most sex chromosome mosaics are thought to arise through errors at anaphase, non-disjunction or lagging on the spindle during early embryogenesis. To explain an XX/XY mosaic in this way several unlikely events would have to take place. The loss of the Y chromosome in an XY zygote by anaphase lag, non-disjunction of the X chromosome in the new XO cell line, and loss of the XO cell line as well as the complementary OO cells would yield an XX/XY mosaic. Theoretically XX and XY cells could also be derived from an XXY zygote through anaphase lag at the first mitotic division affecting both daughter cells. Loss of X in one and Y in the other would give a mixture of XX and XY cells. However dispermic fertilization of an ovum and its polar body or two ova by an X-bearing and a Y bearing spermatozoa seems to be a more likely and less complicated explanation (31) This mechanism would produce a true chimaera since the two cell lines are of different genetic origin This in distinction to mosaicism where the different cell lines originate from a single zygote Chimaerism can be proved only by the demonstration of double parenteral contribution of one or more genetic traits for which the parents are heterozygous. Convincing evidence of XX/XY chimaerism has been established in 3 true hermaphrodites (23 33 54) in one male pseudohermaphrodite (78) and in one apparently healthy blood donor in whom the only sign of an intersex condition was slight gynecomastia (124) The genetic evidence for chimaerism in these cases has mainly been the demonstration of a double population of genetically different erythrocytes (23, 33 78, 124) but double haptoglobin phenotype (23 54) and double phosphoglucomutase types (23) have also been observed. Striking patchiness of skin pigmentation (23 124) and heterochromia of the iris (33) might be suggestive clinical features of chimaerism. The results of different genetic marker analyses employed in the present study did not reveal any inconsistencies suggestive of chimaerism in any of the three XX/XY mosaic patients.

The XX cell line was in minority in all these patients and only one of them was sex chromatin positive in cells from buccal smears. A similar low percentage of XX cells was observed in the case described by Overzier (83) and that studied by Zuelzer and coworkers (124) However in the latter case chimaerism was proven by the demonstration of a double population of erythrocytes. To explain the quantitative disparity between the XX and XY cell lines Zuelzer and his associates put forward the hypothesis that it could be a result of the fertilization of the egg by a Y-bearing sperm and a polar body by an X-bearing sperm (124) Paucity of cytoplasm needed to furnish mass and nutrients for the early cell divisions and perhaps other unfavourable factors affecting a fertilized polar body was assumed to cause a lag in its growth behind the more favoured product derived from the fertilization of the normal pronucleus.

Although the number of reported XX/XY mosaic patients is far less than that of XO/XY mosaicism, these reports indicate that the gonadal and phenotypic expression of XX/XY mosaicism covers as wide a spectrum as that of XO/XY (Table 4) Most of the reported cases have been examples of true hermaphroditism and 10 such cases have been reported between 1962 and 1968 (93) Cases 1 of the present study and two previously reported patients (23 83) fit well into the concept of mixed gonadal dysgenesis. The two other patients (cases 2 and 3) and that reported by Myhre et al. (78) might be classified as male pseudohermaphrodites.

There is now a growing tendency to

mains that mixed gonadal dysgenesis may have other causes than sex chromosome aberrations. Other sex chromosome complements encountered in mixed gonadal dysgenesis include XO (6 14 26) XO/Xy (22 39) XO/Xy/XXy (85) XO/XX/XY (97) XY/XX/XXY (20) XO/XXXY (115) XO/XX/XY/XXY (101) and XO/isoY/isoYY (64). It has not been possible to equate any particular clinical picture with any of these specific chromosome constitutions.

Most patients with mixed gonadal dysgenesis have been reared as females. Of the 40 cases with XO/XY mosaicism 25 were assigned female sex at birth and 15 male (Table 5). Most of these females exhibited some ambisexual development of the external genitalia including phallic enlargement presence of a urogenital sinus and varying degree of labio-scrotal fusion. In most instances the testis was located intraabdominally and individuals with the testis in inguinal or scrotal position were usually assigned male sex at birth.

Severe degree of hypospadias associated with uni or bilateral cryptorchidism has been an almost constant finding in males with mixed gonadal dysgenesis irrespective of sex chromosome constitution (4 14 20 39 42 45 47 48 50 55 64 67 83 94 95 101 123). The only exceptions were an XO/XY mosaic patient reported by Morishima and Grumbach who presented with a penile urethra and unilateral undescended testis (77) and a 14-month old boy reported by Warkany Chu and Kunder who had an XO/XXXY mosaic and presented with an hypoplastic penis and unilateral cryptorchidism (115).

Male pseudohermaphroditism with bilateral testes is a less frequent manifestation of XO/XY mosaicism than mixed gonadal dysgenesis. Including case 4 and case 5 a total of 13 such patients in whom the testicular nature of the gonads has been established by histological examination has been reported (32 50 53 72 90 91 104 112). In contrast to the circumstances in mixed gonadal dysgenesis the majority of these patients have been assigned male sex at birth (Table 5). The masculinizing effect of bilateral testes is also apparent by the fact that one of these patients showed complete lack of Müllerian remnants (50) as opposed to the findings in mixed gonadal dysgenesis where such remnants are a constant finding at least on the side of the streak gonad (12 123). However it is important to realize that even the presence of bilateral testes in the scrotum or the inguinal canal does not preclude the possibility of persistence of Müllerian structures. This was the case in one of our patients (case 5) and has also been observed in two other cases (91 104). Severe hypospadias has been a prominent feature in all patients reared as males, and hypospadias might be the only immediate sign of intersexuality (28 32, 50 91 104).

Short stature with or without the association of some of the somatic features of Turner's syndrome has been a frequent finding in patients with XO/XY mosaicism, although less pronounced than commonly found in Turner's syndrome associated with X chromosome monosomy (32 47 50 53 91 104). Short stature is the most constant clinical finding in Turner's syndrome. The other somatic anomalies might be present to various extent but could also be completely absent. The absence or presence in only slight degree, of phenotypic manifestations has especially been noted in cases where the X monosomy has been present in mosaicism (77). Clinical experience in patients with structural anomalies on the X chromosome indicate that short stature and other somatic effects of Turner's syndrome can be produced by loss however caused of the short arm of the X chromosome only whereas the gonadal dysgenesis can be produced by loss of either arm (1 27 46). It has been suggested that the Y chromosome contains loci homologous to those on the short arm of the X which explains the modifying influence of a Y chromosome on the phenotypic manifestations of Turner's syndrome in individuals with XO/XY mosaicism. It is to be emphasized

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exclude patients with dysgenetic testes due to chromosomal abnormalities from this notion, and restrict the term male pseudohermaphroditism to individuals with normal male karyotype and relatively normal embryonic differentiation of their testes (41). However it seems still useful to retain this term to characterize an individual whose gonads are exclusively testes but whose genital ducts and/or external genitalia deviate towards the phenotypic characteristics of the female irrespective of the individual's sex chromosome complement (53, 123) To avoid confusion the sex chromosome constitution might be included in the designation e.g XX/XY male pseudohermaphroditism.

6. Gonadal neoplasm in dysgenetic gonads

The greatly increased prevalence of gonadal neoplasm in dysgenetic gonads merits attention (69 73 111) It has recently been pointed out that the risk of malignant degeneration is particularly high in patients with an XY-stem line whether this is represented as an uniform XY karyotype or in association with an XO- or XX-cell line (8, 30 56, 113) whereas patients with XO Turner syndrome or XX pure gonadal dysgenesis do not share this risk (34 113) Although various types of gonadal germinal tumors have been described in dysgenetic gonads, the gonadoblastoma (98) dysgenetic gonadoma (70) or gonocytoma type III (110) is of special interest since this tumor develops exclusively in patients with gonadal dysgenesis (56, 113) It has been suggested that the gonadoblastoma arises from undifferentiated so-called "neuter" germ cells in embryologically deficient gonads (71) Since the condition is congenital, the impulse to undergo hyperplasia or neoplasia might occur in childhood

There are fairly good estimates of the risk of malignant transformation in gonadal dysgenesis associated with an XY karyotype. Thus Teter and Boczkowski found 7 cases with germinal tumor among 26 women with gonadal dysgenesis. All of these 7 patients proved to have an XY karyotype whereas no patient with normal female karyotype had germ cell neoplasm (113) Barr and coworkers reviewed the literature and found 7 patients with germinal neoplasm among 26 women with XY karyotype and bilateral streak gonads (8)

There are no similar data on the XO/XY mosaic condition. Since this study brought up the question of prophylactic ablation of dysgenetic testes in patients reared as males, it was decided to review the literature with regard to the incidence of gonadal neoplasm in XO/XY mosaic patients (Table 5) The material has been restricted to patients in whom at least one gonad was of testicular nature There were 40 cases of mixed gonadal dysgenesis. Twenty-five patients were reared as females and 9 of these had gonadal tumor (16 38, 56, 74 94 95 109) Among 15 patients reared as males there were 2 cases with tumor (67 94 95) Testicular dysgenesis with bilateral testes was reported in 13 cases, 4 were reared as females and 9 as males (Table 5) In this group there were two cases of gonadal neoplasm (90, 112) Thus the incidence of gonadal neoplasm in mixed gonadal dysgenesis was 27.5 per cent, in testicular dysgenesis 15 4 per cent, and the overall incidence 24.5 per cent. To some extent the frequency of neoplasia might be exaggerated since cases with tumor might be more likely to be reported On the other hand, there are many cases in which the gonad had been completely destroyed by the neoplastic process, so that the nature of the original gonad could not be determined. Some of these gonads might well have been dysgenetic testes but nevertheless missed in this material.

The localization and classification of the tumors have been summarized in Table 6 The tumor was bilateral in 4 cases. Seminomas were more frequent than gonadoblastomas. The neoplastic process occurred before puberty in 5 cases. Two of the 4 reported gonadoblastomas occurred in this age group It is also note

RANGE OF PHENOTYPIC AND GONADAL EXPRESSION IN XX/XY MOSAICISM

AUTHOR	BLOOD xx/xy	PHENOTYPE: EXT GENITALIA	PHENOTYPE: GENITAL DUCTS	GONADS
BAIN & SCOTT (1965)	19/67	FEMALE WITH PRIMARY AMENORRHEA	TUBE \ UTERUS / TUBE	STREAK — DYS GERMINOMA
REPORTED (1962 1968)	10 CASES OF TRUE HERMAPHRODITISM			OVARY — TESTIS OR OVOTESTIS
OVERZIER (1964)	2/50	AMBIGUOUS	TUBE \ UTERUS / TUBE	ABSENT — TESTIS WITH GONADO BLASTOMA
DENYS & al (1967)	9/15	AMBIGUOUS	TUBE \ UTERUS / TUBE	TESTIS — ABSENT
PRESENT CASE 1	6/109	HYPOSPADIC MALE	VAS \ UTERUS / TUBE	TESTIS WITH SERTOLI CELLS — ABSENT
PRESENT CASE 2	25/205	HYPOSPADIC MALE	VAS — VAS	TESTIS EMBRYONIC — TESTIS EMBRYONIC
PRESENT CASE 3	15/201	HYPOSPADIC MALE	VAS — VAS	TESTIS — TESTIS WITH SPERMATOGENESIS
MYHRE & al (1965)	27/24	HYPOSPADIC MALE	VAS — VAS	TESTIS — TESTIS WITH SPERMATOGENESIS
ZUELZER & al (1964)	15/235	MALE WITH GYNECOMASTIA	VAS — VAS	TESTIS — TESTIS WITH SPERMATOGENESIS

Table 4

exclude patients with dysgenetic testes due to chromosomal abnormalities from this notion, and restrict the term male pseudohermaphroditism to individuals with normal male karyotype and relatively normal embryonic differentiation of their testes (41) However it seems still useful to retain this term t characterize an individual whose gonads are exclusively testes but whose genital ducts and/or external genitalia deviate towards the phenotypic characteristics of the female irrespective of the individual's sex chromosome complement (53 123) To avoid confusion the sex chromosome constitution might be included in the designation e.g XX/XY male pseudohermaphroditism

4. Gonadal neoplasm in dysgenetic gonads

The greatly increased prevalence of gonadal neoplasm in dysgenetic gonads merits attention (69 73 111) It has recently been pointed out that the risk of malignant degeneration is particularly high in patients with an XY-stem line whether this is represented as an uniform XY karyotype or in association with an XO- or XX-cell line (8, 30, 56, 113) whereas patients with XO Turner's syndrome or XX pure gonadal dysgenesis do not share this risk (34 115) Although various types of gonadal germinal tumors have been described in dysgenetic gonads, the gonadoblastomas (98) dysgenetic gonadoma (70) or gonocytoma type III (110) is of special interest since this tumor develops exclusively in patients with gonadal dysgenesis (56, 113) It has been suggested that the gonadoblastoma arises from undifferentiated, so-called neuter' germ cells in embryologically deficient gonads (71) Since the condition is congenital the impulse to undergo hyperplasia or neoplasia might occur in childhood

There are fairly good estimates of the risk of malignant transformation in gonadal dysgenesis associated with an XY karyotype. Thus Teter and Boczkowski found 7 cases with germinal tumor among 26 women with gonadal dysgenesis. All of these 7 patients proved to have an XY karyotype whereas no patient with normal female karyotype had germ cell neoplasm (113) Barr and coworkers reviewed the literature and found 7 patients with germinal neoplasm among 26 women with XY karyotype and bilateral streak gonads (8)

There are no similar data on the XO/XY mosaic condition Since this study brought up the question of prophylactic ablation of dysgenetic testes in patients reared as males, it was decided to review the literature with regard to the incidence of gonadal neoplasm in XO/XY mosaic patients (Tabl 5) The material has been restricted to patients in whom at least one gonad was of testicular nature There were 40 cases of mixed gonadal dysgenesis. Twenty-five patients were reared as females and 9 of these had gonadal tumor (16 38, 56 74 94 95 109) Among 15 patients reared as males there were 2 cases with tumor (67 94 95) Testicular dysgenesis with bilateral testes was reported in 13 cases, 4 were reared as females and 9 as males (Table 5) In this group there were two cases of gonadal neoplasm (90, 112) Thus the incidence of gonadal neoplasm in mixed gonadal dysgenesis was 27.5 per cent, in testicular dysgenesis 15 4 per cent, and the overall incidence 24.5 per cent. To some extent the frequency of neoplasia might be exaggerated since cases with tumor might be more likely to be reported On the other hand there are many cases in which the gonad had been completely destroyed by the neoplastic process, so that the nature of the original gonad could not be determined. Some of these gonads might well have been dysgenetic testes, but nevertheless missed in this material

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ZUELZER & al (1964)	15/235	MALE WITH GYNECOMASTIA	VAS / VAS	TESTIS / TESTIS WITH SPERMATOGENESIS

Table 4

Gonads	TOTAL	NUMBER OF CASES
STREAK OR ABSENT — TESTIS	6	5 SEMINOMAS; 1 EMBRYONAL CARCINOMA
STREAK — TESTIS	3	1 SEMINOMA; 2 GONADOBLASTOMA
TESTIS — TESTIS	2	1 UNILATERAL GONADOBLASTOMA; 1 BILATERAL GONADOBLASTOMA
STREAK — TESTIS (OR)	2	1 SEMINOMA (INTRA ABD); 1 SEMINOMA (SCROTAL)

Fig. 32. Schematic presentation of some clinical findings in reported cases of gonadal tumor associated with XO/XY mosaicism and mixed gonadal dysgenesis, or testicular dysgenesis.

MIXED GONADAL DYSGENESIS	NUMBER OF CASES REPORTED	WITH TUMOR	
(Testis & streak)			
REARED AS FEMALES	25	9	
REARED AS MALES	15	2	
	40	11	27 5 Per cent
TESTICULAR DYSGENESIS			
(Two testes)			
REARED AS FEMALES	4	1	
REARED AS MALES	9	1	
	13	2	15 4 Per cent
TOTAL	53	13	24 5 Per cent

Table 5 Reported cases of gonadal tumors in XO/XY mosaicism in which at least one gonad was of testicular nature.

CLASSIFICATION OF TUMOR (Total number of cases)	LOCALIZATION OF TUMOR Testis	Streak	Bilateral Streak & Testis	Bilateral Two Testes
SEMINOMA (8)	5	2	1	
GONADOBLASTOMA (4)	1		2	1
EMBRYONAL CARCINOMA (1)	1			

OCCURRENCE IN A TESTIS 11 CASES
BEFORE PUBERTY 5
AFTER PUBERTY 4
AGE NOT STATED 4

SEMINOMA 3 CASES
GONADOBLASTOMA 2

Table 6 Classification and localization of gonadal tumors in XO/XY mosaicism in which at least one gonad was of testicular nature.

Management

It will be both impractical and unfortunate to regard hypospadias, as such as a form of intersex. However it seems apparent that the condition merits more attention from pediatricians than has commonly been given in the past, and that any hypospadias, apart from the glandular and penile type in patients with both gonads in the scrotum, warrants the exclusion of an intersex condition.

The diagnostic approach includes a careful family and maternal history. The family history is important in revealing hereditary forms of hypospadias. Special attention should be given to the possible presence of the salt losing form of congenital virilizing adrenal hyperplasia. In such families there might be a history of siblings who died shortly after birth with symptoms of vomiting and dehydration. The mother should be asked about drug ingestion during the first trimester of pregnancy with special reference to any hormone treatment. It is our impression that woman is not likely to report a pregnancy test with progestins as drug ingestion unless especially questioned on this point. It might also be relevant to explore the possibility of continued use of oral contraceptives after conception.

If no testes are palpable in the scrotum in a newborn infant with hypospadias, the child must be suspected of having abnormal genital development and further studies to determine the exact sex must be undertaken. If cells from buccal smears are sex chromatin positive, it is highly probable that the infant is a female pseudohermaphrodite due either to congenital virilizing adrenal hyperplasia or maternal progestin treatment. The finding of elevated urinary excretion of 17 ketosteroids and pregnantriol confirms the former diagnosis, whereas normal hormone excretion and a maternal history of progestin therapy sustains the latter. These studies should be made as promptly as possible after birth to avoid erroneous assignment of sex with all its psychologic and medical calamities.

The result of this study and the clinical findings in reported cases of intersex conditions associated with chromosome aberrations imply that the presence of glandular or penile hypospadias in patients with both testes in the scrotum merits no further investigation of the patient's sex. However in penoscrotal scrotal or perineal hypospadias such investigations are mandatory whether or not the testes are palpable in the scrotum and should include chromosome analysis. Patients with hypospadias of these categories should only be considered hypospadic males when intersex conditions have been ruled out. Sex chromatin determination in buccal smears is not sufficient under these circumstances since many sex chromosome aberrations would escape detection by this method either because cell lines with two or more X chromosomes are not present, or are represented in too low proportion to give a significant number of sex chromatin positive cells.

There remains a group of patients characterized by the presence of glandular or penile hypospadias associated with unilateral cryptorchidism. This group

worthy that 3 of the tumors in the pre pubertal group were classified as semi nomas since this type of neoplasm is considered to be very rare in childhood (71)

Some of the clinical findings in the patients have been outlined in Figure 32 In all cases with tumor there were rem nants of Müllerian structures to various extent. The tumor aroused more often in testicular tissue than in streak gonads When a streak was the site of the tumor there was also a tumor in the contralateral testis or the testis was located in the scrotum All tumors except for a semi noma in a streak gonad were located intra abdominally

The data in Table 5 might give an impression that the incidence of neoplastic transformation of dysgenetic testes is lower in patients reared as males than females However this might be a func tion of the practise of assignment of sex at birth, since the presence of gonads in scrotum or in a labioscrotal fold seems to be the most decisive single factor in the assignment of the male gender role. Therefore, intraabdominally located testes probably carry the same risk regardless of sex of rearing

It is possible that high gonadotropin levels play some etiologic role in the neoplastic transformation of dysgenetic gonads (41 71) In this respect it is noteworthy that this stimulation of the target cells might be present from early childhood as demonstrated in cases 1 and 2 in the present report

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psychologic nature may be anticipated (76). Reassignment of sex after 18 months of age should therefore only be undertaken as an exception. Individual cases of *female pseudohermaphroditism* due to congenital virilizing adrenal hyperplasia might constitute such exceptions, since these patients can be converted with proper treatment into normal fertile women.

In all these conditions the question of what to tell the patient and/or when and what to tell the parents is important. No rules can be laid down and much depends on the nature of the case and the knowledge and profession of patients and parents. In most instances the parents should be given an explanation, with the aid of simple diagrams, that up to certain stages of embryonic life the gonads and other organs are the same in both sexes and only gradually complete their differentiation in the male or female pattern. The concept of "incomplete development" is then easy to comprehend, truthful, and helpful in the explanation. Discussions on the intricacies of chromosome aberrations are apt to cause both confusion and perturbation. Of the different factors that constitute an individual's gender role and identity the genetic or chromosomal sex, *per se* is probably the least important. However full comprehension of this and full acceptance of an aberration may be very difficult, and therefore the actual sex chromosome complement need not be divulged.

Many parents have an unexpressed fear that their child would have psychosexual problems and are relieved when reassured that there need be no such problems or abnormal sexual behavior provided the child is properly and consistently raised in the appropriate gender role.

was only represented by three patients in the present material and these constellations are probably not very common At present it is not possible to give well founded recommendations for this group The probability of sex chromosome aberration is certainly highest in the more severe degrees of hypospadias and is enhanced by concomitant cryptorchidism On the other hand intersex conditions associated with XO/XY mosaicism have been described in patients with penile urethra and cryptorchidism (77 115) Conceivably there are intermediate forms between these extremes and it therefore seems reasonable to carry out chromosome analysis in patients with the milder degrees of hypospadias when these are associated with unilateral cryptorchidism

If an abnormality of the sex chromosome constitution has been established, an explorative laparotomy with gonadal biopsies must be performed to determine the exact nature of the intersex condition and for the purpose of excision of any contradictory sexual structures Before resorting to laparotomy however as much information as possible should be obtained concerning the possible existence of a vaginal pouch or a urogenital sinus communicating with the urethra

Although Müllerian structures have no physiologic action in the absence of ovaries it has been the practice to remove such structures in patients reared as males because it is of paramount psychological importance to assure the parents or adolescent patients that no contradictory sex structure exists (52) The probability of malignant degeneration in such structures is probably low although an adenocarcinoma of the body of the uterus has been reported in a 45-year old XO/XY male pseudohermaphrodite (67) Removal of a vagina which communicates with the urogenital sinus is a tedious and difficult procedure which is probably unnecessary since it *has caused no* problem when left behind (52)

The risk of malignant degeneration in dysgenetic gonads *whenever* a Y chromosome is present in the sex chromosome complement has been discussed to some length in the previous section. The conclusions to be drawn are

1 That streak gonads should be removed regardless of their location.
2 Testes located in the scrotum should be preserved.
3 At present it seems prudent to recommend prophylactic ablation of intraabdominally located testes in most cases. These testes are invariably sterile (52 119) The gonad should be preserved only if it is represented by a relatively normally appearing testis, without adjacent Müllerian structures, which could be relocated in the scrotum.

It is to be reemphasized that it is most important that a firm and rational decision is made as early as possible with regard to the gender role to which an infant with ambiguous external genitalia is best adapted In male pseudohermaphroditism this decision should largely depend upon the size of the phallus and the anatomy of the external genitalia and less on the testicular nature of the gonads If the phallus is sufficiently well developed to function reasonably well as a penis it seems rational to raise the infant as a male It is then essential to correct the hypospadias in early childhood, since the most important male function performed as children is to urinate while standing

In some male pseudohermaphrodites the phallus is so rudimentary and poorly developed that there is no hope of constructing an adequate functioning penis It is probably preferable to raise these patients as females (12 52 53 119)

Children assigned to a totally inappropriate sex give rise to the very complex problem whether to change the sex of rearing or to leave matters undisturbed *The decision is largely dependent* upon the age of the child and the degree to which the gender role has been established *Money Hampson and Hampson* have shown that a change is feasible until the age of 18 months, and is sometimes successful until 30 months of age, but thereafter serious consequences of

psychologic nature may be anticipated (76) Reassignment of sex after 18 months of age should therefore only be undertaken as an exception. Individual cases of female pseudohermaphroditism due to congenital virilizing adrenal hyperplasia might constitute such exceptions, since these patients can be converted with proper treatment into normal fertile women.

In all these conditions the question of what to tell the patient and/or when and what to tell the parents is important. No rules can be laid down and much depends on the nature of the case and the knowledge and profession of patients and parents. In most instances the parents should be given an explanation with the aid of simple diagrams, that up to certain stages of embryonic life the gonads and other organs are the same in both sexes and only gradually complete their differentiation in the male or female pattern The concept of "incomplete development" is then easy to comprehend, truthful and helpful in the explanation Discussions on the intricacies of chromosome aberrations are apt to cause both confusion and perturbation Of the different factors that constitute an individual's gender role and identity the genetic or chromosomal sex, *per se* is probably the least important However full comprehension of this and full acceptance of an aberration may be very difficult, and therefore the actual sex chromosome complement need not be divulged.

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Summary

The results of experimental embryology indicate that hypospadias may result from deficient fetal testicular function. In view of these findings it seemed of interest to study hypospadic patients with special reference to pathogenetic mechanisms which might have interfered with testicular differentiation and/or function during fetal life.

The material consisted of 80 hypospadic patients. All were reared as males and the majority had been referred for reconstructive surgery of the hypospadias. Thirty two cases were classified as glandular hypospadias, 24 as penile, 18 as penoscrotal and 6 as scrotal. Cordae to various extent, were present in all patients. Hypospadias was associated with unilateral undescended testis in 8 cases, and in 2 cases there was bilateral cryptorchidism.

In 5 cases there was a history of maternal progestin treatment in early pregnancy. Among these patients there was one penoscrotal hypospadias, whereas the other 4 had hypospadias of the penile type. When the position of the urethral meatus was compared to the week of gestation at which progestin treatment was started there seemed to be a relationship with the more proximal openings in the infants of mothers who had been treated in the first month of pregnancy.

It is probable that maternal progestin treatment may affect human fetal genital development by inhibiting the activity of fetal 3β-hydroxysteroid dehydrogenase enzyme, and thereby mimicking the genital anomalies observed in both sexes in congenital virilizing adrenal hyperplasia associated with 3β-hydroxysteroid dehydrogenase deficiency.

Chromosome analysis was carried out in all patients. A normal male karyotype was found in all cases of glandular hypospadias. In the penile group there was one patient with a normal female karyotype. This was a 2 9/12 year old girl with congenital virilizing adrenal hyperplasia who was thought to be a cryptorchid hypospadic boy. Her sex of rearing was changed to female.

In the remaining groups there were 3 patients with an XX/XY mosaic and 2 patients with an XO/XY mosaic. The abnormal karyotypes tended to occur among the patients with the severest degrees of hypospadias and especially when associated with undescended testes. However there were 3 mosaic patients with both gonads present in the scrotum. One of the XX/XY patients had mixed gonadal dysgenesis with remnants of Müllerian structures. In the other two XX/XY mosaic cases there were no Müllerian remnants. Histologic examination of gonadal tissue in one of these patients revealed severely embryonic structures with persistence of the coelomic epithelium. The XO/XY mosaic patients had both dysgenetic testes and remnants of Mullerian structures. A normal male karyotype was found in one patient with mixed gonadal dysgenesis who presented with penoscrotal hypospadias and unilateral cryptorchidism.

Thus a pathogenetic mechanism which conceivably could operate through a

reduction of fetal testicular function has been unveiled in 11 out of 79 male hypospadic patients studied, or in 14 per cent of cases. Since the more severe forms of hypospadias were overrepresented in the material and because glandular hypospadias has a particular embryogenesis, it might be justified only to consider the more severe forms. It then appears that some evidence of impairment in fetal testicular function was uncovered in 11 out of 48 patients, or in 21 per cent of cases.

Urinary excretion of testosterone and estrogens were measured in the six male patients with intersex conditions before and after the administration of 1500 I U of HCG twice weekly for 3 weeks and suppression of the adrenal cortex with 2 mg of dexamethasone for the last two days of the treatment period. The base values for estrogens were within normal range for age, and did not increase following HCG stimulation. The mean urinary excretion of testosterone under basal condition was 4.0 ± 3.8 µg per 24 hours which was not significantly different from a mean value of 2.3 ± 1.7 µg per 24 hours found in 13 normal prepubertal boys. The testosterone excretion did not increase significantly after HCG treatment. This finding suggests that a relative deficiency to secrete testosterone might persist postnatally.

Two of the six intersex patients excreted considerable amounts of FSH. In both these cases histological examination of testicular tissue showed absence of spermatogenesis, whereas spermatogenesis was present in the other patients. The significance of this finding in relation to FSH regulation in the male has been discussed.

The clinical and cytogenetic findings in the intersex cases have been discussed with special reference to present concepts of embryonal differentiation of the gonads, gonaducts, and external genitalia. The increased prevalence of gonadal neoplasm in dysgenetic gonads whenever an XY-stem line is present in the sex chromosome complement has been emphasized.

It would be both impractical and unfortunate to regard hypospadias, as such, as a form of intersex. However it seems apparent that the condition merits more attention from pediatricians than has generally been given in the past. Guide lines for the diagnostic work up of hypospadic patients and for the therapeutic approach to the different intersex conditions encountered have been outlined.

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LORA N THOMAS AND RONALD R. ROGERS

ALMQVIST & WIKSELL STOCKHOLM SWEDEN

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by

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Almqvist & Wiksells
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Retrospective studies of growth of breastfed infants in technically advanced societies are most difficult to interpret. The ready availability and convenience of alternate methods of feeding constitute a strong motivation to discontinue breast feeding in instances in which there is even minor question about its adequacy. Thus, infants identified retrospectively as having been entirely or predominantly breastfed for 4 or 5 months represent a highly selected group and the size and nature of the population from which the observed group has been drawn are unknown.

Few prospective studies of breastfed babies have been reported from technically advanced countries. The present report concerns growth and serum chemical determinations of 149 infants enrolled in such a study. In instances in which an infant failed to complete the planned 112 days of observation, the circumstances of his withdrawal have been recorded and data on his performance to the time of withdrawal from the study are presented.

It was hoped that performance of these breastfed infants would be useful as reference data for performance of other breastfed infants and of infants fed other diets. In addition, there was reason to believe that the method of approach (frequent observations at precisely defined ages) would enlarge our knowledge of normal variations in rates of growth and various serum chemical values during the first few months of life.

SUBJECTS AND INTERVALS OF STUDY

Normal fullterm Caucasian infants with birth weights of 2,500 gm or more were considered eligible for enrollment in the study. Nearly all were children of students or younger staff members of the University of Iowa and several were siblings of children who had served as subjects of other studies reported from the Infant Metabolic Unit in recent years. The dates of birth of the infants were March 10, 1965 to October 7, 1968. All were enrolled in the program during the first 9 days after birth. Each infant received a stipend of $10 per month for the period of study.

The infants were weighed and measured between 6 and 9 days of age, within 2 days of each of the following ages: 14, 28, 42 and 56 days, and within 4 days of ages 84 and 112 days.

In describing mean size and change in size of the infants (Appendix A, Table 1 and Figure 1), recorded measurements were corrected by parabolic interpolation or extrapolation utilizing three adjacent values to reflect values applicable to ages 8, 14, 28, 42, 56, 84 and 112 days. For convenience, these same age designations have been employed throughout although data on serum chemical determinations have not been so corrected.* The mean value for total protein at age 28 days, for *example*, represents the mean of results pertaining to infants between 26 and 30 days of age.

FEEDING

At the time an infant was enrolled in the study his mother was interviewed by one of us (L.N.T.), details of the program were outlined and written instructions were provided. A ready-to-feed formula (Similac, 67 kcal/100 ml) was supplied in 120 or 240 ml disposable units to provide one supplementary feeding daily although not all mothers elected to feed this. All infants received a supplement providing, in daily dose of 0.6 ml, 400 I.U. of vitamin D and 0.5 mg of fluoride as the stannous salt. At 30 days of age an additional supplement was introduced (Fer-In-Sol)[1] which provided

[1] Kindly supplied by Mead Johnson and Company, Evansville, Ind.

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15 mg of elemental iron daily as ferrous sulfate

Although introduction of one strained food (oatmeal with bananas and applesauce) was permitted at age 28 days, another (pears) at age 56 days and two additional foods (apple sauce bananas) at age 84 days, no attempt was made to encourage feeding of foods other than human milk. Parents of experimental subjects were advised that addition of such foods to the diet was optional and that breast feeding plus the supplements already mentioned constituted a complete diet. Strained foods were purchased from those prepared by one manufacturer [1]

PROCEDURES AND METHODS

Weight was determined to the nearest 5 gm with infant scales [2] Length was measured as described by Fomon (1 a) utilizing a measuring board with fixed head piece and movable foot piece Two examiners measured each subject, one holding the head against the headboard while the other stretched the lower extremities, pressed the footboard firmly against the soles of the feet and noted body length The two examiners then exchanged positions, repeated the procedure, and the average of the two measurements was recorded When results of the two examiners differed by more than 0 4 cm, a measurement was made by a third examiner and the two values agreeing more closely were utilized.

Blood for serum chemical determinations was obtained by venipuncture of the external or internal jugular vein With few exceptions, 6 ml of blood was obtained between 1 00 and 1 30 p.m. there was no restriction relating to the time of feeding.

Concentration of total protein in serum was determined by the biuret method and was standardized with control sera which were in turn standardized by determinations of nitrogen using the Dumas method Separation of serum proteins into the various fractions was carried out by electrophoresis as described by the Beckman Instrument Company (2) on cellulose acetate using the Beckman Microzone Electrophoresis Cell, Model R 101 Scanning of the cellulose acetate membranes was performed with the Beckman Analytrol, Model RB using the Microzone Scanning Attachment, Model R 102, with speed control set at 30

Concentrations of calcium and magnesium in serum were determined by atomic absorption spectroscopy (3 4) after dilution of the serum with a solution of lanthanum oxide in hydrochloric acid (to a final concentration of 1 % lanthanum) which serves to suppress phosphorus interference in determination of calcium concentration. Concentration of phosphorus in serum was determined by a micro modification of the method of Fiske & Subba Row (5) and alkaline phosphatase activity by the method of Nothstein & Ellerbrook (6) Urea nitrogen concentration of serum was determined as described by Conway (7) Triglyceride concentration was determined by the method of Van Handel & Zilversmit (8) as modified by Van Handel (9) Concentration of cholesterol was determined by the method of Carr & Drekter (10)

RESULTS

One hundred and-forty nine subjects, 83 males and 66 females, were enrolled in the study and 70 % 58 males and 46 females, completed the planned 112 days of observation. An attempt was made to determine the reasons that 45 infants failed to complete the study Families of 5 infants (subjects 262, 274 359 360 and 389) moved from the city In eight instances, breast feeding was terminated or interrupted for a prolonged period because of illness of either mother or infant, necessitating elimination of the infant from the study Two mothers were admitted to the hospital (the mother of subject 323 for cholecystectomy and the mother of subject 1 011 for psychiatric treatment) The mother of subject 1 006 reported that milk

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[1] Gerber Products Company Fremont, Mich.
[2] Continental Scales Company Chicago, Ill.

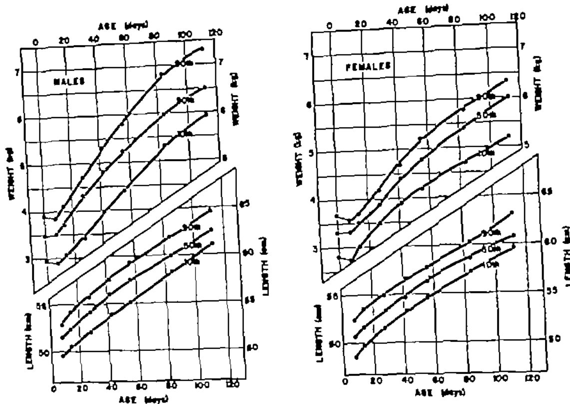


Fig. 1 Weights and lengths of 58 male and 46 female breastfed infants during the first 112 days of life. The 10th, 50th, and 90th percentiles are shown

supply became inadequate during an episode of influenza-like disease. The mother of subject 368 discontinued nursing because the infant developed oral moniliasis which did not readily respond to treatment. Two infants (subjects 318 and 386) had diarrhea and one (subject 380) had "infection" at the time breast feeding was discontinued. One infant (subject 281) was admitted to the hospital for surgery (correction of premature cranial synostoses) The other 32 infants were eliminated from study because the mother or the family physician judged the milk supply to be inadequate or less commonly the infant for reasons unknown to us failed to appear for a scheduled appointment.

A study (11) carried out concurrently in the Department of Obstetrics and Gynecology at the University of Iowa and employing some of the same subjects suggests that maternal use of oral contraceptives may have interfered with lactation in a substantial percentage of women who received such medication (see Discussion)

Whether or not mothers of the infants were receiving oral contraceptive medications was known for 39 of the 40 infants enrolled in the present study after October 13 1967 Four of the 39 infants (subjects 386, 389 1 006 and 1,011) failed to complete 112 days of study for reasons already identified that seemed unrelated to oral contraceptive medications. Mothers of 24 of the remaining 35 infants did not receive oral contraceptive medications and in each instance the infant completed 112 days of study Mothers of 11 of the 35 infants received oral contraceptive medications with only 4 of the infants completing 112 days of study

Size Data, length and weight

The Appendix provides tabular data on length and weight of each infant. Fig. 1 indicates the

15 mg of elemental iron daily as ferrous sul fate

Although introduction of one strained food (oatmeal with bananas and applesauce) was permitted at age 28 days, another (pears) at age 56 days and two additional foods (apple sauce bananas) at age 84 days no attempt was made to encourage feeding of foods other than human milk. Parents of experimental subjects were advised that addition of such foods to the diet was optional and that breast feeding plus the supplements already mentioned constituted a complete diet Strained foods were purchased from those prepared by one manufacturer [1]

PROCEDURES AND METHODS

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[2] Continental Scales Company Chicago Ill.

Table 1 (cont.)

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
14 days	5th			18.1	22.4	23.0	21.2	20.8
	10th			24.0	26.5	28.2	25.0	21.8
	25th			34.0	32.5	31.9	29.7	26.7
	50th			40.2	39.4	37.4	33.0	30.9
	75th			49.2	46.9	43.8	36.5	33.2
	90th			57.0	51.8	49.0	41.6	36.4
	95th			60.7	55.1	51.0	44.7	40.8
28 days	5th				21.9	21.4	18.9	17.6
	10th				26.0	23.4	22.0	21.0
	25th				31.8	30.0	27.2	24.4
	50th				40.4	35.5	30.9	29.0
	75th				46.1	42.0	36.3	32.5
	90th				52.1	47.5	42.4	35.7
	95th				53.1	50.5	43.8	39.4
42 days	5th					15.1	16.3	15.6
	10th					17.3	20.2	18.4
	25th					24.4	23.1	21.9
	50th					34.7	28.8	26.3
	75th					40.4	33.5	30.1
	90th					48.4	39.9	36.0
	95th					52.4	42.7	38.7
56 days	5th						15.0	15.0
	10th						15.9	17.5
	25th						22.1	20.0
	50th						25.8	24.8
	75th						33.3	28.1
	90th						39.4	35.1
	95th						41.6	37.0
84 days	5th							11.8
	10th							13.6
	25th							17.3
	50th							22.4
	75th							27.7
	90th							33.8
	95th							35.1
Length Females								
8 days	5th		0.1	0.9	1.0	0.9	0.8	0.8
	10th		0.3	0.9	1.1	1.0	0.9	0.9
	25th		1.3	1.1	1.2	1.1	1.0	0.9
	50th		1.6	1.4	1.3	1.2	1.1	1.0
	75th		2.2	1.6	1.4	1.3	1.2	1.1
	90th		2.8	1.8	1.5	1.4	1.3	1.2
	95th		3.7	1.9	1.5	1.5	1.3	1.2
14 days	5th			0.5	0.8	0.8	0.8	0.8
	10th			0.6	0.9	0.9	0.9	0.8
	25th			0.9	1.0	1.0	0.9	0.9
	50th			1.2	1.2	1.1	1.0	1.0
	75th			1.6	1.3	1.2	1.2	1.1
	90th			1.8	1.4	1.3	1.2	1.2
	95th			1.9	1.5	1.4	1.3	1.[illegible]
28 days	5th				0.4	0.6	0.7	0.7
	10th				0.6	0.8	0.8	0.8
	25th				0.9	0.9	0.9	0.8
	50th				1.2	1.1	1.0	0.9
	75th				1.4	1.2	1.1	1.1
	90th				1.6	1.3	1.2	1.1
	95th				1.7	1.4	1.3	1.1

Table 1 *Daily change in length (mm/day) and weight (gm/day) between selected ages*

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Length Males								
8 days	5th		0.6	0 8	0.9	0.9	1 0	0.9
	10th		0 7	0 9	1 0	1.0	1 0	1 0
	25th		1.2	1.2	1.2	1.2	1 0	1 0
	50th		1 6	1 4	1.3	1.2	1 1	1 1
	75th		2.3	1 6	1 5	1.3	1.2	1 1
	90th		2.9	1 8	1 6	1 4	1.3	1.2
	95th		3 1	1.9	1 7	1.5	1 4	1.3
14 days	5th			0 7	0 8	0.9	0 9	0.9
	10th			0.8	0.9	0.9	0 9	1 0
	25th			1 0	1 1	1 1	1 0	1 0
	50th			1.2	1.2	1.2	1 1	1 1
	75th			1.5	1.5	1.3	1.2	1 1
	90th			1 7	1 6	1 4	1.2	1.2
	95th			1 8	1 7	1.5	1.3	1.2
28 days	5th				0 6	0.8	0.9	0.9
	10th				0.8	0.9	0.9	0.9
	25th				1.0	1 1	0.9	0.9
	50th				1.3	1 1	1 1	1.0
	75th				1 4	1.2	1 1	1 1
	90th				1 7	1 4	1 3	1.2
	95th				2.0	1 7	1 4	1.2
42 days	5th					0 4	0 7	0 8
	10th					0.6	0.8	0.9
	25th					0.8	0.9	0.9
	50th					1 1	1 0	1 0
	75th					1.2	1 1	1 1
	90th					1.5	1.2	1 1
	95th					1 7	1 4	1.2
56 days	5th						0 6	0.8
	10th						0 7	0 8
	25th						0 8	0.9
	50th						1 0	1 0
	75th						1 1	1 1
	90th						1.3	1 1
	95th						1 4	1.2
84 days	5th							0.5
	10th							0.6
	25th							0.8
	50th							1 0
	75th							1 1
	90th							1.3
	95th							1 4
Weight Males								
Birth	5th	−36.1	−7 7	8 3	14 6	18.9	20.5	20 7
	10th	−31.3	−5 7	11 5	18 7	21 1	22.5	22.5
	25th	−15 4	5 0	18 4	24 0	26.2	26 1	24.9
	50th	− 3 7	13 6	28.0	30 8	30.8	29 0	28.0
	75th	7.2	22.7	33 7	37 4	37 3	33.8	30.6
	90th	16.3	28 8	39 8	43 3	43 0	37.9	34 9
	95th	25.5	37 1	46.5	45 4	44.2	42.0	38.1
8 days	5th		10 6	19.2	22.7	22.1	22.2	22.0
	10th		13 2	24 4	27 5	27.5	4 4	23 1
	25th		23 8	31.2	32.1	31.3	29 5	27.5
	50th		40 1	39 0	39 0	36.5	33.3	31 6
	75th		47.2	48 0	47.5	44 6	37.2	33 6
	90th		58.6	54 0	50.3	48 6	43 6	37.3
	95th		67.3	58.1	53.2	51.2	46.1	41 4

Table I (cont.)

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
14 days	5th			18.1	22.4	23.0	21.2	20.8
	10th			24.0	26.5	28.2	25 0	21.8
	25th			34.0	32.5	31.9	29 7	26.7
	50th			40.2	39 4	37 4	33 0	30.9
	75th			49.2	46.9	43.8	36.5	33.2
	90th			57 0	51.8	49 0	41 6	36.4
	95th			60.7	55.1	51.0	44 7	40.8
28 days	5th				21.9	21 4	18.9	17.6
	10th				26.0	23.4	22.0	21.0
	25th				31.8	30 0	77.2	24 4
	50th				40 4	35.5	30.9	29.0
	75th				46.1	42.0	36.3	32.5
	90th				52.1	47.5	42.4	35 7
	95th				53.1	50.5	43.8	39 4
42 days	5th					15 1	16.3	15 6
	10th					17.3	20.2	18.4
	25th					24 4	23.1	21.9
	50th					34 7	28.8	26.3
	75th					40.4	33.5	30 1
	90th					48.4	39 9	36.0
	95th					52.4	42.7	38 7
56 days	5th						15.0	15.0
	10th						15.9	17.5
	25th						22.1	20.0
	50th						25.8	24.8
	75th						33.3	28 1
	90th						39 4	35 1
	95th						41 6	37 0
84 days	5th							11.8
	10th							13.6
	25th							17.3
	50th							22.4
	75th							27 7
	90th							33.8
	95th							35 1
Length Females								
8 day	5th		0.1	0.9	1.0	0.9	0.8	0.8
	10th		0.3	0.9	1 1	1.0	0.9	0.9
	25th		1.3	1 1	1.2	1 1	1.0	0 9
	50th		1 6	1 4	1.3	1.2	1 1	1.0
	75th		2.2	1.6	1 4	1.3	1.2	1 1
	90th		2 8	1.8	1.5	1 4	1.3	1.2
	95th		3.7	1.9	1.5	1.5	1.3	1.2
14 days	5th			0.5	0.8	0.8	0.8	0 8
	10th			0.6	0.9	0.9	0.9	0.8
	25th			0.9	1.0	1.0	0.9	0.9
	50th			1.2	1.2	1 1	1.0	1.0
	75th			1.6	1.3	1.2	1.2	1 1
	90th			1.8	1 4	1.3	1.2	1.2
	95th			1.9	1.5	1 4	1.3	1.2
28 days	5th				0.4	0 6	0 7	0.7
	10th				0.6	0.8	0.8	0.8
	25th				0.9	0.9	0.9	0.8
	50th				1.2	1.1	1.0	0.9
	75th				1 4	1.2	1 1	1 1
	90th				1.6	1.3	1.2	1 1
	95th				1 7	1.4	1.3	[illegible]

Table 1 (*cont.*)

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
42 days	5th					0.3	0.6	0.6
	10th					0.5	0.7	0.7
	25th					0.7	0.9	0.8
	50th					1.0	1.0	0.9
	75th					1.2	1.1	1.0
	90th					1.5	1.1	1.1
	95th					1.6	1.2	1.1
56 days	5th						0.6	0.6
	10th						0.6	0.7
	25th						0.8	0.8
	50th						1.0	0.9
	75th						1.1	1.0
	90th						1.3	1.1
	95th						1.4	1.1
84 days	5th							0.4
	10th							0.5
	25th							0.7
	50th							0.8
	75th							1.0
	90th							1.1
	95th							1.3
Weight Females								
Birth	5th	−25.2	−5.5	8.2	11.5	14.0	16.2	17.2
	10th	−20.9	−1.5	12.9	18.5	19.4	18.4	17.9
	25th	−16.4	4.9	19.3	22.2	22.4	22.3	21.0
	50th	−3.3	12.9	25.6	27.3	26.8	25.3	23.7
	75th	16.2	21.3	29.9	31.4	31.5	29.2	27.2
	90th	23.0	30.3	31.6	34.7	33.4	31.4	29.2
	95th	27.7	33.1	36.9	38.5	36.4	32.2	31.6
8 days	5th		5.2	17.4	19.0	16.9	18.6	18.9
	10th		12.0	21.6	23.7	23.2	21.3	19.9
	25th		18.0	29.5	28.0	26.3	24.0	23.2
	50th		32.4	33.1	32.8	30.6	27.5	25.8
	75th		44.5	40.0	38.2	36.4	33.1	29.2
	90th		49.5	47.5	45.2	40.6	34.6	31.7
	95th		59.4	51.1	47.8	43.9	35.7	33.9
14 days	5th			17.2	17.8	15.3	18.8	18.3
	10th			20.4	25.0	23.1	20.3	19.5
	25th			29.4	28.4	26.3	23.2	22.2
	50th			35.9	33.0	30.6	28.3	25.7
	75th			41.0	39.1	36.8	32.8	28.6
	90th			47.6	42.3	39.5	34.7	31.4
	95th			52.2	47.7	43.4	36.2	34.9
28 days	5th				12.9	15.8	16.4	15.7
	10th				17.4	17.5	17.9	16.7
	25th				24.9	22.3	21.0	20.7
	50th				32.9	29.6	26.8	24.7
	75th				37.9	35.5	29.8	26.7
	90th				43.2	38.4	33.1	29.9
	95th				51.3	42.4	36.3	33.7
42 days	5th					11.3	15.0	13.0
	10th					14.9	16.2	16.4
	25th					18.8	19.4	18.8
	50th					24.4	4 7	23.1
	75th					33.7	28.5	25.1
	90th					37.1	31.4	28.4
	95th					45.1	35.6	34.9

Table 1 (cont.)

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
56 days	5th						11 7	11.5
	10th						14.2	15.3
	25th						19.3	17.3
	50th						23 8	22.0
	75th						27.5	24.0
	90th						31 4	27 7
	95th						32.1	34.2
84 days	5th							8.2
	10th							10.5
	25th							16.7
	50th							19
	75th							23.3
	90th							28.7
	95th							33.3

10th, 50th and 90th percentiles for lengths and weights of male and female infants who completed 112 days of observation.

Incremental Data. length and weight

Infants who completed 112 days: Table 1 provides data on gains in length and weight during various age intervals for those infants who completed 112 days of observation. In interpreting these data it may be noted (Table 1) that the 10th percentile values for gain in weight of male infants during the consecutive 14-day intervals, 14 to 28 28 to 42, and 42 to 56 days of age are 24 0 26.0 and 17.3 gm/day respectively However the 10th percentile value for gain in weight for the entire interval 14 to 56 days is 28.2 gm/day a larger daily gain than the 10th percentile value for any of the constituent 14-day intervals. This observation indicates that infants who gained most slowly during one 14-day interval were not, in the majority of instances, those who gained most slowly during the subsequent 14-day interval.

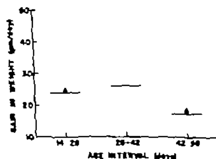


Fig. Patterns of weight gain of three individual infants in relation to the 10th percentile values for 58 male breastfed infants. ——— 10th percentile rates of gain for the designated 14-day intervals; 10th percentile rate of gain for the entire 42-day interval from 14 to 56 days of age. Each symbol refers to the performance of one infant: ●, subject 279 ○ subject 307 ▲, subject 320. For discussion, see text.

Examples of the variability of patterns of gain in weight of individual infants may be seen from Fig. 2. Subject 279 gained at a rate less than the 10th percentile value during the intervals 14 to 28 and 28 to 42 days but at a rate considerably greater than the 10th percentile value during the interval 42 to 56 days His rate of gain for the entire interval from 14 to 56 days was 29.5 gm/day a value greater than the 10th percentile. A rather common pattern of weight gain was that exhibited by subject 307 whose rate of gain was less than the 10th percentile value during one of three 14-day intervals and whose gain for the entire 42-day interval was well above the 10th percentile (actually in this case, at about the 25th percentile) A less common pattern of weight gain is that exhibited by subject 320 whose rate of gain was slightly above the 10th percentile value for each of the 14-day intervals but was well below the 10th percentile value for the entire interval from 14 to 56 days.

Table 1 (cont)

Interval	Percentile	8 days	14 days	28 days	42 days	56 days	84 days	112 days
42 days	5th					0.3	0.6	0.6
	10th					0.5	0 7	0.7
	25th					0.7	0 9	0 8
	50th					1 0	1 0	0.9
	75th					1.2	1 1	1 0
	90th					1.5	1 1	1 1
	95th					1 6	1.2	1 1
56 days	5th						0 6	0.6
	10th						0 6	0 7
	25th						0.8	0.8
	50th						1 0	0.9
	75th						1 1	1 0
	90th						1.3	1 1
	95th						1 4	1 1
84 days	5th							0 4
	10th							0.5
	25th							0 7
	50th							0.8
	75th							1.0
	90th							1 1
	95th							1.3
Weight Females								
Birth	5th	−25.2	−5 5	8.2	11.5	14 0	16.2	17.2
	10th	−20.9	−1 5	12.9	18.5	19 4	18.4	17.9
	25th	−16.4	4.9	19 3	22.2	22.4	22.3	21 0
	50th	−3.3	12.9	25 6	27 3	26.8	25 3	23 7
	75th	16.2	21.3	29.9	31 4	31.5	29.2	27.2
	90th	23.0	30.3	31 6	34 7	33 4	31 4	29.2
	95th	27 7	33 1	36.9	38.5	36 4	32.2	31 6
8 days	5th		5.2	17 4	19 0	16.9	18 6	18.9
	10th		12.0	21 6	23 7	23.2	21 3	19.9
	25th		18.0	29 5	28 0	26.3	24 0	23.2
	50th		32.4	33 1	32.8	30.6	27.5	25 8
	75th		44.5	40.0	38.2	36 4	33 1	29.2
	90th		49 5	47.5	45.2	40.6	34 6	31 7
	95th		59 4	51 1	47 8	43 9	35 7	33 9
14 days	5th			17.2	17 8	15.3	18.8	18.3
	10th			20 4	25 0	23 1	20 3	19.5
	25th			29 4	28 4	26.3	23.2	22.2
	50th			35 9	33 0	30.6	28.3	25 7
	75th			41 0	39 1	36.8	32.8	28.6
	90th			47 6	42.3	39 5	34 7	31 4
	95th			52 2	47 7	43 4	36.2	34 9
28 days	5th				12.9	15 8	16.4	15 7
	10th				17 4	17.5	17 9	16.7
	25th				4.9	22.3	21 0	20.7
	50th				32.9	29 6	26.8	24 7
	75th				37 9	35 5	29 8	26.7
	90th				43.2	38.4	33.1	29.9
	95th				51 3	42.4	36.3	33 7
42 days	5th					11 3	15 0	13 0
	10th					14 9	16.2	16 4
	25th					18 8	19 4	18.8
	50th					24 4	24 7	23 1
	75th					33 7	28.5	25 1
	90th					37 1	31 4	28 4
	95th					45 1	35 6	34.9

formed with sera of both 112-day-old and 56-day-old infants, and beginning in December 1966, with sera of all infants. Data on total proteins are reported only for sera with which electrophoretic analysis was also carried out.

Concentrations of total proteins and albumin were noted to increase with increasing age and there appeared to be some tendency for concentrations of $alpha_1$ and $alpha_2$ globulin to increase also. On the other hand, with increasing age, concentrations of gamma globulins steadily decreased in males. In females the concentrations decreased between 28 and 56 days of age but increased between 56 and 112 days of age. The difference in mean concentration of gamma globulin at 112 days of age was statistically significant at the 95% level of confidence. Possibly the ability to synthesize gamma globulins develops earlier in female than in male infants, explaining, in part, their greater resistance to infection in the early months of life.

Concentrations of cholesterol and triglycerides were greater in sera of female than in sera of male infants and the differences were statistically significant at the 95% level of confidence at 28, 84 and 112 days of age for cholesterol and at 28 and 112 days of age for triglycerides.

Results reported here are in general agreement with those reported previously with respect to serum concentrations of urea nitrogen (1 *b*), calcium and phosphorus (1 c). Mean activities of serum alkaline phosphatase at various ages were greater for males than for females and the difference was statistically significant at the 95% level of confidence at 28 and 56 days of age. Concentrations of magnesium in serum over the period of observation demonstrated neither age-related nor sex-related differences.

In only a few instances were statistically significant differences found between mean serum chemical values of infants who completed and of those who did not complete 112 days of study. At age 56 days, 5 females of the incomplete series had a mean concentration of triglycerides of 173 mg/100 ml (standard deviation, 52) compared with a mean value of 112 mg/100 ml (Table 2) in the complete series. Similarly at age 84 days, male infants of the incomplete series demonstrated lower mean concentration of $alpha_2$ globulins (6 infants, mean 0.61 gm/100 ml, S.D. 0.11), higher mean concentration of urea nitrogen (11 infants: mean 9.6 mg/100 ml, S.D. 6.0) and lower mean concentration of magnesium (11 infants: mean 2.0 mg/100 ml, S.D. 0.2). In each instance the difference was statistically significant at the 95% level of confidence, but in view of the small number of determinations in the incomplete series, biologic significance seems unlikely.

DISCUSSION

As mentioned previously, 83 males and 66 females were enrolled in the study. This greater enrollment of male than of female infants is not readily explained. Possibly women are more inclined to breast feed male infants. Alternatively, mothers of breastfed infants may be more inclined to enroll a male infant than to enroll a female infant in a study of this type. A separate study is currently in progress to determine whether sex of the infant influences the mother's decision to breast feed.

Since sex-related differences in infancy are well recognized with respect to size, rate of growth, body composition (13), susceptibility to infection (14, 15) and a number of non-infectious diseases (e.g. pyloric stenosis), it is not surprising that the present study should demonstrate statistically significant sex related differences in concentrations of gamma globulin, cholesterol, triglycerides and alkaline phosphatase. We have noted even greater sex-related differences in serum cholesterol concentrations of 2-week-old and 4-week-old sow reared piglets (16). The need to investigate the fundamental physiologic processes responsible for these differences is obvious.

As already mentioned, little interpretation of data pertaining to breastfed infants is possible on the basis of retrospective results. In the

Table 2. *Serum chemical values of normal breastfed infants*[a]

Concentration per 100 ml of serum	Age 28 days			Age 56 days			Age 84 days			Age 112 days		
	N	Mean	S.D	*N*	Mean	S.D	*N*	Mean	S.D	*N*	Mean	S.D
Males												
Total protein (gm)	22	5.87	0.50	36	5.96	0.42	29	6.16	0.57	51	6.29	0.51
Albumin (gm)	22	4 02	0.35	36	4 14	0.34	?9	4.27	0.39	51	4.38	0.40
Globulins (gm)												
alpha	22	0 14	0 03	36	0 17	0 03	29	0 18	0.03	51	0 17	0 04
alpha$_1$	22	0 53	0 10	36	0.60	0 11	29	0 74	0 14	51	0.81	0 19
beta	22	0 61	0 11	36	0.67	0 13	29	0 69	0.20	51	0 67	0.11
gamma	22	0.57	0 14	36	0.38	0.09	29	0.28	0 08	51	0.26	0.10
Cholesterol (mg)	21	139	31	32	153	34	25	133	32	47	145	26
Triglycerides (mg)	18	122	36	32	106	57	25	170	76	46	148	57
Urea Nitrogen (mg)	43	8 5	3.2	49	6.6	2.1	47	7 0	2.7	51	7.3	4.2
Calcium (mg)	41	10.2	0 8	47	10.3	1 0	42	10.4	0 8	48	10.3	0.8
Phosphorus (mg)	43	6.6	0 7	49	6 4	0 7	47	6.2	0.5	49	6.2	0.7
Alkaline phosphatase[b]	31	22	6	40	21	7	35	21	8	44	18	7
Magnesium (mg)	40	2.0	0.2	47	2.1	0.2	45	2.1	0.2	50	2.2	0.2
Females												
Total protein (gm)	18	6.04	0 40	27	5.86	0 44	21	6.21	0.57	42	6.31	0 62
Albumin (gm)	18	4 07	0.27	27	4 03	0.35	21	4.29	0.37	42	4.36	0 42
Globulins (gm)												
alpha	18	0 15	0 02	27	0 17	0 04	21	0 17	0 03	42	0.19	0.04
alpha$_1$	18	0 55	0 07	27	0 65	0 12	21	0 74	0.18	4.	0 78	0 17
beta	18	0 70	0 18	27	0 63	0 11	1	0 71	0 13	42	0 67	0.16
gamma	18	0.57	0.10	27	0.38	0 10	21	0.30	0.06	42	0.31	0.10
Cholesterol (mg)	13	180	35	25	157	37	?0	155	29	40	165	36
Triglycerides (mg)	9	157	43	24	112	53	18	195	56	38	170	52
Urea Nitrogen (mg)	37	8.3	.3	33	6.4	2.2	40	6.4	2.2	42	6.6	3.5
Calcium (mg)	37	10 3	0 8	33	10.3	0 8	40	10.3	0.8	42	10.7	0.7
Phosphorus (mg)	39	6.9	0 8	33	6.4	0.8	40	6.1	0.7	42	6.1	0 7
Alkaline phosphatase	31	19	5	28	17	5	32	17	5	36	17	5
Magnesium (mg)	39	2.0	0.4	32	2.0	0.2	40	2.1	0.2	41	2.1	0.3

Bold figures indicate that value is greater than the corresponding value for infants of the opposite sex and that the difference is statistically significant at the 95% level of confidence.
[b] King Armstrong units.

Individual patterns of gain in length and weight for any of the 149 infants in the study can be calculated on the basis of data provided in the Appendix

Infants who failed to complete 112 days Mean rates of gain in weight by males who completed 112 days of study were 39 1 33 2 and 27 1 gm/day during the age intervals 8 to 42 42 to 56 and 56 to 84 days Corresponding rates of gain by male infants who failed to complete 112 days of study were 37 2, 24 8 and 24 5 gm/day The differences in rates of gain in weight were statistically significant (12) for the interval 42 to 56 days ($p < 0.01$) but not for the other two intervals. During these age intervals, mean rates of gain in weight (33 1 26 1 and 23.5 gm/day) by female infants who completed 112 days of study were not significantly different from those (31 1 27 8 and 20 5 gm/day) by female infants who failed to complete 112 days of study

Serum chemical determinations

Table 2 summarizes results of chemical determinations with sera of infants who completed 112 days of study

Until January 1966 electrophoretic separation of proteins was performed only with sera of 112-day-old infants Between January and December 1966 electrophoresis was per

formed with sera of both 112-day-old and 56-day-old infants, and beginning in December 1966, with sera of all infants. Data on total proteins are reported only for sera with which electrophoretic analysis was also carried out.

Concentrations of total proteins and albumin were noted to increase with increasing age and there appeared to be some tendency for concentrations of alpha and alpha$_2$ globulin to increase also On the other hand, with increasing age, concentrations of gamma globulins steadily decreased in males In females the concentrations decreased between 28 and 56 days of age but increased between 56 and 112 days of age The difference in mean concentration of gamma globulin at 112 days of age was statistically significant at the 95% level of confidence Possibly the ability to synthesize gamma globulins develops earlier in female than in male infants, explaining, in part, their greater resistance to infection in the early months of life

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Results reported here are in general agreement with those reported previously with respect to serum concentrations of urea nitrogen (1 *b*) calcium and phosphorus (1 c) Mean activities of serum alkaline phosphatase at various ages were greater for males than for females and the difference was statistically significant at the 95% level of confidence at 28 and 56 days of age Concentrations of magnesium in serum over the period of observation demonstrated neither age-related nor sex-related differences.

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United States at present approximately one woman in four breast feeds her infant during the first few days of his life but less than one woman in 10 persists in breast feeding until the infant reaches the age of four months (1 d) If as one may suspect, women are more likely to persevere in breast feeding when no problems are encountered and to change from breast to bottle feeding when difficulties arise the infants who are breastfed to age 3 or 4 months will be likely to represent a highly selective group

In the present study an attempt was made to avoid a high dropout rate No infant was enrolled if the parents seemed to have any hesitance about joining the study if they seemed likely to move from the city before the infant reached 112 days of age or if the mother planned to work outside of the home. In addition a monthly stipend was provided Nevertheless, the dropout rate was 30% In 13 instances (approximately 9% of infants enrolled in the study) the family moved from the city or illness occurred in the mother or infant. The study of Miller & Hughes (11) previously cited suggests that discontinuation of breast feeding in a number of other instances may have been related to use of oral contraceptive medication by the mothers Among primiparas in that study (the data most easy to interpret) 14 of 21 (67%) who received placebos but only 9 of 36 (25%) who received oral contraceptive medications breastfed their infants until 12 weeks of age When the infants were weighed before and after the first breast feeding of the day it was found that infants of primiparas who were receiving placebos gained more weight during feeding than did those whose mothers were receiving oral contraceptives

Unfortunately incomplete data are available on use of oral contraceptive medications by mothers of infants in the present study Nevertheless, it was apparent that after October 1967 the dropout rate was considerably higher among infants whose mothers did than among those who did not receive oral contraceptive medications

It may therefore be acceptable to conclude that infants completing 112 days of breast feeding in this study were representative of infants in the community who were initially breastfed, who did not have more than minor illness, whose mothers were strongly motivated to continue breast feeding until the infant reached 112 days of age and were not receiving oral contraceptive medications. Even this limited interpretation of the data must be employed with caution. Knowledge that an infant was breastfed and received no more than one bottle (240 ml) of formula daily and a limited assortment of pureed foods is clearly an inadequate description of the total diet. With respect to protein intake, for example 240 ml of formula was likely to provide between 1 0 and 1 7 gm more protein than the equivalent volume of human milk On the other hand, if the mother had not offered any formula feeding but had been liberal in feeding the designated pureed foods, protein intake would have been less than with breast feeding alone

If one is willing to accept as a reference the performance of the infants who completed 112 days of observation the data can be of use in judging performance of individual breastfed infants observed in other situations. For example, the information that more than 10% of normal breastfed infants have not yet regained birth weight by 14 days of age (Table 1) may be of practical value The 10th percentile rates of gain between various ages may be of particular usefulness since it seems reasonable to maintain close supervision of infants growing at rates less rapid than 90% of normal breastfed infants. In this regard, attention is called to distinct sex related differences in rates of growth and to the important effect of age In the 28-day interval from 14 to 42 days of age, the 10th percentile rate of gain in weight for males was 26.5 gm/day while in the 28-day interval from 84 to 112 days of age, the 10th percentile value was only 13 6 gm/day

Since we have little knowledge of those factors that motivate one woman to breast feed her infant and another to select bottle feeding,

It is clear that we have little reason to assume that a population of breastfed infants enrolled in a study (even though enrolled at birth) is closely similar to a population of infants in the same community whose mothers do not elect to breast feed. Nevertheless, performance of normal breastfed infants nursed by healthy well nourished mothers seems useful as reference data for considering the performance of infants receiving commercially available or experimental diets. An example of such application is provided by a previous study (17) in which infants were fed an experimental formula (29B) relatively low in protein. Mean intakes of protein of males and females were 1.80 and 1 61 gm/kg/day respectively (standard deviations 0 18 and 0 18) during the interval 8 to 42 days of age, and 1.57 and 1 45 gm/kg/day (standard deviations 0 17 and 0 10) during the interval 42–112 days of age. Since rates of growth in length and weight and serum concentrations of albumin were nearly identical to those reported here, performance of infants fed the experimental formula could be assessed as "normal" and one might conclude that the requirement for protein was no greater than the amounts ingested.

SUMMARY

One-hundred-and-forty-nine normal fullterm infants were enrolled during the first 9 days after birth in a study of breastfed infants 104 (70%) completed the planned 112 days of observation. Lengths and weights at 8, 14 28, 42, 56, 84 and 112 days of age are presented for each infant. Rates of gain in length and weight between various ages are summarized and some patterns of growth of individual infants are discussed. Serum chemical data at 28, 42, 56, 84 and 112 days of age are presented. Statistically significant sex related differences in serum concentrations of cholesterol and triglycerides (greater in females than in males) and alkaline phosphatase (greater in males than in females) are demonstrated.

It is suggested that these data on performance of normal infants breastfed by healthy mothers may be useful for evaluating the performance of other breastfed infants and of infants fed commercially available or experimental formulas.

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If one is willing to accept as a reference the performance of the infants who completed 112 days of observation, the data can be of use in judging performance of individual breastfed infants observed in other situations For example, the information that more than 10% of normal breastfed infants have not yet regained birth weight by 14 days of age (Table 1) may be of practical value The 10th percentile rates of gain between various ages may be of particular usefulness since it seems reasonable to maintain close supervision of infants growing at rates less rapid than 90% of normal breastfed infants In this regard, attention is called to distinct sex related differences in rates of growth and to the important effect of age In the 28-day interval from 14 to 42 days of age, the 10th percentile rate of gain in weight for males was 26.5 gm/day while in the 28-day interval from 84 to 112 days of age the 10th percentile value was only 13 6 gm/day

Since we have little knowledge of those factors that motivate one woman to breast feed her infant and another to select bottle feeding,

it is clear that we have little reason to assume that a population of breastfed infants enrolled in a study (even though enrolled at birth) is closely similar to a population of infants in the same community whose mothers do not elect to breast feed. Nevertheless, performance of normal breastfed infants nursed by healthy well-nourished mothers seems useful as reference data for considering the performance of infants receiving commercially available or experimental diets. An example of such application is provided by a previous study (17) in which infants were fed an experimental formula (29B) relatively low in protein. Mean intakes of protein of males and females were 1.80 and 1 61 gm/kg/day respectively (standard deviations 0 18 and 0 18) during the interval 8 to 42 days of age, and 1.57 and 1 45 gm/kg/day (standard deviations 0 17 and 0 10) during the interval 42–112 days of age. Since rates of growth in length and weight and serum concentrations of albumin were nearly identical to those reported here, performance of infants fed the experimental formula could be assessed as "normal" and one might conclude that the requirement for protein was no greater than the amounts ingested.

SUMMARY

One-hundred-and-forty-nine normal fullterm infants were enrolled during the first 9 days after birth in a study of breastfed infants, 104 (70%) completed the planned 112 days of observation. Lengths and weights at 8, 14 28 42, 56, 84 and 112 days of age are presented for each infant. Rates of gain in length and weight between various ages are summarized and some patterns of growth of individual infants are discussed. Serum chemical data at 28 42, 56, 84 and 112 days of age are presented. Statistically significant sex related differences in serum concentrations of cholesterol and triglycerides (greater in females than in males) and alkaline phosphatase (greater in males than in females) are demonstrated.

It is suggested that these data on performance of normal infants breastfed by healthy mothers may be useful for evaluating the performance of other breastfed infants and of infants fed commercially available or experimental formulas

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APPENDIX

Lengths (cm) of Breastfed Infants at Various Ages

Subject number	Birth date	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Complete Series—Males								
276	3 31 65	52.0	53.9	55.1	56.8	58.5	60.8	64.0
277	4 4 65	52.0	52.8	54.8	56.4	57.8	59.8	62.6
278	5 1 65	52.3	52.8	54.4	56.4	57.6	60.3	62.4
279	5 6 65	51.5	52.1	53.2	54.4	56.3	59.4	61.7
291	6 8 65	50.4	52.4	53.3	54.8	56.6	58.3	61.5
292	6 12.65	49.9	51.7	53.7	54.9	56.4	58.6	61.1
293	7 13 65	51.5	53.0	54.7	56.5	58.3	60.7	63.2
295	8.20 65	51.3	52.3	54.5	56.0	57.7	60.5	62.4
296	9 18 65	55.2	56.2	58.0	59.4	61.1	64.1	65.8
297	10 5 65	49.8	51.6	53.4	55.7	57.0	59.9	63.0
298	10.22.65	50.4	51.7	53.1	54.0	55.2	58.6	62.1
299	10.24 65	52.6	53.6	54.6	55.5	57.2	59.9	62.0
300	10.26 65	52.5	52.5	54.0	55.8	57.5	59.8	62.3
301	10.25 65	52.2	53.3	54.4	56.6	59.0	62.0	64.6
303	11.27 65	51.8	52.4	53.3	56.6	58.1	61.0	64.1
305	12.29 65	51.2	52.3	54.0	55.6	57.2	60.0	62.5
306	12.30 65	52.5	53.9	55.4	57.3	59.4	61.9	64.2
307	1 19 66	50.3	51.0	53.0	55.8	56.3	58.6	60.7
309	3 4 66	52.1	54.3	55.8	57.4	58.9	62.0	63.9
320	3.24 66	49.6	50.4	52.0	53.8	55.2	58.3	61.2
322	5 2.66	50.9	52.3	53.8	55.7	57.4	60.0	61.7
324	5.27 66	52.2	53.1	54.6	56.2	57.8	60.0	63.8
325	6 3 66	51.5	52.7	54.6	57.0	58.5	61.3	64.4
326	6.13 66	53.2	54.2	56.8	58.5	60.0	62.2	65.0
327	7 4 66	51.9	52.7	55.2	56.8	57.6	61.0	63.8
329	9 9 66	51.5	52.0	54.2	56.4	57.2	60.2	62.8
340	10 14 66	52.7	54.2	55.7	56.7	58.4	60.8	63.4
342	11 9 66	50.3	51.2	53.1	54.9	55.4	59.7	62.6
343	12. 6.66	49.5	50.5	52.4	53.8	55.9	59.7	61.7
344	12. 9 66	50.6	51.5	53.4	56.0	57.1	59.2	62.2
345	12.15 66	48.6	49.3	50.5	52.2	52.8	56.0	58.6
346	12.18 66	53.0	53.5	55.4	57.2	58.9	61.9	63.4
348	2.28.67	52.3	52.3	54.2	56.2	57.8	61.0	64.2
361	3 30 67	52.8	54.0	55.5	57.4	59.2	61.5	63.7
362	4 6.67	47.6	48.0	49.2	50.7	52.0	54.6	58.1
365	6. 7 67	50.5	51.4	53.3	55.5	56.3	59.3	62.0
369	9.30 67	51.2	51.6	53.6	54.8	55.3	58.8	61.2
381	10 8 67	53.2	53.8	56.4	58.5	60.5	64.2	64.7
383	10 13 67	52.1	53.0	54.6	57.8	59.6	61.9	65.0
385	10 18.67	51.7	52.6	54.6	56.5	58.1	60.9	63.2
387	11 9 67	51.4	52.8	54.5	56.1	57.6	59.6	62.3
388	11 14 67	52.4	53.2	55.3	56.4	57.8	61.4	63.3
1001	11 19 67	51.7	52.6	54.0	54.6	57.6	59.3	63.3
1002	11.26.67	49.2	50.8	53.1	54.9	56.1	58.3	62.4
1003	12. 9 67	53.6	54.7	57.1	58.3	60.0	64.1	65.0
1007	3 17 68	48.8	49.2	51.5	53.7	54.8	57.9	62.2
1010	5 20 68	49.7	50.7	51.8	53.6	54.8	57.1	60.1
1012	6 15 68	53.6	54.2	56.8	58.5	60.1	61.9	65.9
1013	6.17 68	50.8	51.7	54.1	55.2	55.5	58.3	60.8
1014	7 5 68	52.4	53.2	55.2	57.5	58.4	60.3	63.5
1015	8 3 68	50.2	52.0	53.3	54.7	56.5	59.1	[illegible]
1016	8 12.68	49.8	51.3	51.8	54.5	55.4	59.2	61.6
1017	9 1 68	50.5	51.4	53.7	54.7	56.3	58.9	61.7
1018	9 13 68	52.1	53.3	54.8	56.6	57.8	59.8	63.0
1019	9 15 68	50.8	51.1	52.7	54.3	57.0	58.8	61.5
1020	9 17 68	49.1	50.6	52.8	54.9	57.0	59.9	62.7
1021	9.21 68	52.6	54.3	55.6	57.3	58.8	61.1	62.4
1022	9.21 68	50.9	52.4	53.6	55.4	56.8	59.9	62.9
Incomplete Series—Males								
274	3 10 65	48.8	50.8	53.0	54.9	55.9	58.7	
302	11 15 65	51.3	52.1	54.2	56.1	58.1	60.6	
304	12. 7 65	53.2	53.3	54.3				

Appendix (cont.)

Subject number	Birth date	8 days	14 days	28 days	42 days	56 days	84 days	112 days
308	2.19.66	50.5	50.8	53.2	55.8	56.9	60.6	
321	4.24.66	49 7	50.1	51.5	53.8	55.3	57.0	
323	5 7 66	52.9	54 7	56.3	57.5	58.2		
329	7.16.66	48.1	50.8	51 7	53.6	55.3	56.5	
347	1 7.67	50.4	51 1	52.9	55.0	56.4	59.8	
349	1. 1.67	52.1	52.6	54.1	55.5	57.9	60.9	
360	3 2.67	50.9	50.8	53.5	55 4	57 1	59.8	
363	5.23.67	53.3	53 6	55.5	56.9	58.7	60.8	
364	5 29 67	49.3	50 1	52.8	54 2			
366	7.25 67	50.2	51.2	52.8	54 7	55.9		
368	9.21.67	52.4	54.0	54.9	57 1	58.6		
380	10 8.67	48.3	49.5	51 6	53.5	54 9		
384	10.13.67	49.2	50.2	51 4	53.5	53 7		
386	10.30.67	53.6	54 8	56.1				
389	11 15.67	50.3	51.6	53.3	54 7	56.1		
1004	12.13.67	50 0	50.9	53.5	54.5	55.5		
1005	12.30 67	55.0	55.5	57 6	59 6	60.5	62.6	
1006	12.30.67	53 0	54.1	55.2	56.9	59 0		
1008	4.27 68	50 4	51 4	53.2	55 4	57.2		
1009	5.21.68	53 5	53.9	55.9	57.2	59.0	62.4	
1011	6. 9.68	49 5	50.9	53.0	54.6	55.2		
1023	10. 7 68	50.6	51 7	53.2				
Complete Series—Females								
263	4 2.65	50.8	51 6	52.7	55 1	56.5	59.3	61 7
264	4 29 65	51 4	51 7	53.8	55.8	56.[illegible]	57 7	59.9
268	6. 3.65	50.7	51.5	53 7	54.5	55 4	57.0	59.5
280	9 1 65	53.2	54 1	56 4	57.8	58.9	62.3	64 4
282	9 13.65	50.8	50.9	53.4	54.2	56.3	57.8	59.9
283	10.16 65	49 6	52.0	52.7	54 4	55.9	58.4	61.5
284	10.29.65	50 7	51 6	53 4	54.9	56.6	59 4	61 4
287	11.29.65	47.5	48.9	51.2	52.9	55.2	58.3	60 0
288	12. 1.65	50.4	51 7	52.6	53.2	54.3	57 4	59 7
289	12. 9 65	51.5	51.9	53.9	55.5	57 1	59 7	62.2
310	2.23 66	48.9	50.4	52.4	54 3	55.2	57.6	60.1
312	3 11.66	51.0	51.9	53.9	54.6	56.6	58.0	60.2
313	4.15.66	47 1	49 0	51 8	52.2	54.3	56 2	60.0
315	5 17 66	51.3	52.5	53.6	55.3	57 7	60 1	63.0
317	5.28.66	49 7	50 7	52.9	54 7	56.5	59.3	62.1
330	6 16.66	50.5	51 4	52.2	53.8	55 0	57 7	60.4
331	6.24 66	51.8	52.2	53.5	55.5	56 6	58.6	60 6
332	6 30.66	50.7	53.1	53 7	55.5	56.7	59 1	61 1
333	7 12.66	48.5	49 3	52.0	53 1	55.4	57.6	59.8
334	7.21 66	49 7	51.5	52.3	53.7	55 1	57.9	59.9
335	8. 3.66	50.3	50.8	53.6	54 4	55.5	59.0	60.5
337	9.21 66	50.8	51.9	53.6	55.2	56 8	60.7	62.2
339	12. 9.66	48.5	49 7	51.3	53.3	55 1	58.1	61 1
350	12.17 66	48.3	49 9	51.5	52.9	53.7	56.9	59 7
352	12.28 66	49 5	49 7	51 7	53 7	54.7	58.2	61.1
353	1 4 67	51.2	52.2	54.1	56 0	57.4	60 2	63 7
354	1 13 67	53 7	54 6	56.6	57.8	59 1	61 7	63.3
355	1 17.67	50.2	50.3	51 9	54.3	55.4	58.9	61.0
358	2 17 67	48.6	49 6	51.5	53.5	55 1	57 7	60 4
370	4. 8 67	50 6	51.5	52.7	54.9	55 4	59 4	62.2
371	4.14 67	49 4	50.9	51.6	53.4	54.2	57.2	58.5
372	4 21.67	51 1	52.2	54.4	55 4	57.0	58.6	60.9
373	4.23 67	49 1	50.2	51 7	53.8	55 4	58.3	60.2
375	5 4 67	52.2	53 7	55.4	57 4	58.5	61.9	63 1
377	7.30 67	51 1	52.0	53.2	55 7	56.3	58.3	60.1
379	10. 7 67	51.8	52.3	54 1	55 7	56.5	60 2	62.5
390	10 15.67	52.2	51.6	55.8	57 0	58 4	61 4	63.2
391	11 3 67	49.9	51.0	53.6	55 1	56.9	59 8	63.0
392	11 12.67	51.5	51.4	53.3	55.0	56.5	59 1	62.7
393	11.26 67	49 4	50.4	52 0	53.5	55.1	57 1	58.8

Appendix (cont)

Subject number	Birth date	8 days	14 days	28 days	42 days	56 days	84 days	112 days
394	12. 6.67	49 0	50 1	51.9	54.2	54 6	58.2	60.2
398	1.30.68	52.3	52.3	54 7	56 1	56.8	59 6	60 4
399	1 31 68	52.6	53 4	55 0	56.6	57 7	59.8	62.8
1100	6.10 68	52.3	53 8	55.2	56 7	58 0	60.2	63.3
1101	6. 9 68	50.5	51 5	52.5	54.3	56.0	58 7	60.2
1102	8.20 68	50 0	51 3	52.9	54 1	56.0	58.5	60.7
Incomplete Series—Females								
262	3 18 65	50.3	51.2	52.4	54.3	55.3	58 1	
264	4.22.65	50.2	51 1	53 4	54 6	55.7	58.7	
265	4.25 65	47.2	48.3	50.6	51 7			
267	5.20 65	49 8	51 7	53.1	54 0	56.5		
269	7.29 65	50 5	50.7	52.4	53 8	55 8	58.3	
281	9 7 65	51 1	53.2	55 1				
286	11.24 65	52.4	53 6	55.3	56.5	58.0	59 7	
314	5 15 66	53 0	54 0	55 3				
316	5 18.66	50 7	51.2	52.4	54.2	55 6		
318	5.30 66	53 1	53 3	54 6	56.5	57.3		
319	6. 2.66	49.9	50 9	52.0				
336	9 12.66	50.1	51 8	53.3	55.3	56.7		
351	12.19 66	50 4	50 7	52.3	53 6			
357	1.23 67	49 9	50.0	51 7	53 4	54 8	57.0	
359	3 8 67	49.0	49.5	51.6	53 1	54.5	57.0	
374	4.22.67	49.2	50.2	52.0	54.3	55 1	57.8	
376	6 10 67	46.4	47 3	48.7	51.2	52.0		
378	8.22.67	52.2	52.5	53 6	55.5			
396	12.17 67	51.8	52.4	54.3	55.3	57 7	60.1	
397	1.23 68	52.9	54.3	55 9	56.6			

Weights (gm) of Breastfed Infants at Various Ages

Subject number	Birth	8 days	14 days	28 days	42 days	56 days	84 days	112 days
Complete Series—Males								
276	3,580	3 900	3,979	4,539	4,881	5,331	5 751	6,309
277	3,280	3,235	3,349	3 862	4,341	4 837	5 456	6,403
278	3,500	3 616	3 859	4,343	4,910	5,327	5 866	6,198
279	3 100	3 025	3 109	3,375	3 715	4 345	5,509	6,356
291	3 470	3 435	3 681	4,175	4 700	5,125	5 678	6,192
292	3,220	3 424	3 844	4,521	5 127	5 695	6,370	6,812
293	3,550	3 435	3 703	4 443	5,009	5 471	6,091	6,584
295	3,670	3,533	3,665	4 175	4,575	4,935	5 765	6,460
296	3 910	3,805	4,082	4 780	5 473	5,984	6,773	7,236
297	3,250	3,320	3,537	4,319	5 107	5,675	6,781	7 625
298	2,960	3 118	3,280	4,020	4 485	4,935	5,790	6 410
299	3 770	3 860	4,065	4,349	4 808	5,250	5,657	6,316
300	3,580	3 480	3 758	4 463	4 770	5,330	6,001	6,381
301	3,250	3 300	3 615	4,234	4 897	5,591	6,525	7 179
303	3 440	3,459	3,534	4 053	4,646	5,210	5 899	6,553
305	3,870	3 620	3 773	4 139	4 617	5 149	6,211	6,959
306	3,540	3,520	3 805	4 141	4 618	5,164	5,977	6,464
307	3 600	3 665	3 734	4,353	4 855	5,065	5,783	6,113
309	4,080	4 009	4 415	5,290	5 875	6,555	7,325	7,985
320	2,920	2,935	2,973	3,318	3,707	3,963	4,390	4 801
322	3 690	3,565	3 807	4,501	5,180	5,914	6,875	7,306
324	3 780	3,802	4 031	4 425	5,000	5,480	6,265	7 115
325	3,200	3 159	3 275	3 720	4,340	4,830	5 455	6,160
326	3,300	3 630	3,906	4 661	5,275	5,779	6,462	7 120
327	3,530	3,400	3 752	4,562	5 111	5,532	6,224	6,949

Appendix (cont.)

Subject number	Birth	8 days	14 days	28 days	42 days	56 days	84 days	112 days
339	3,360	3,321	3 600	4 450	5 180	5 700	6,500	7 175
340	3,760	3 779	4,075	4,565	4,979	5,315	6,105	6,696
342	3,390	3,325	3 435	3 991	4,811	5,052	6,161	6,831
343	2,950	2,720	3,029	3,531	4,268	4,830	5,943	6,463
344	3,980	3,833	4,050	4,440	4,905	5,040	5,500	5,875
345	3,110	2,935	3 101	3,522	4,059	4,515	5,464	5,958
346	3,510	3,615	3,789	4,365	4,729	5,299	5 742	6,320
348	3,630	3,605	3 522	4,040	4,612	5 105	6,078	7,036
361	3,590	3 630	3,870	4,436	4,966	5,381	6,156	6,482
362	2,900	2,750	2,813	2,999	3,411	3,651	4,740	5,618
365	3 470	3,083	3,299	3 791	4,391	4,874	5,521	6,005
369	3,390	3,401	3,645	3,898	4,271	4,464	5 129	5 767
381	3,520	3,650	3,852	4,335	4,967	5,467	6,221	6,948
383	3 610	3,647	4,025	4 725	5 455	6,393	7 153	7 882
385	4,100	3,625	3 734	4,332	5,011	5 791	7,225	8,207
387	3,340	3,245	3 473	4,271	4,923	5 451	5,882	6,732
388	3,530	3,530	3 630	4 429	5 173	5 477	6,298	6,727
1001	4,180	3,905	4,100	4,682	4,854	5,345	6,223	7,583
1002	3,280	3,070	3,382	3,979	4,620	4,965	5,632	6,426
1003	3,970	3 839	4,088	4,738	5,416	5 755	6,415	7 174
1007	2,860	2,596	2,872	3,377	3,962	4,203	4,929	5,999
1010	2,720	2,755	2,938	3,406	3,691	3,902	4,441	5,040
1012	3,900	3 879	4,179	4,812	5,493	6,012	7,018	7,562
1013	3,410	3,533	3,796	[illegible]	4,705	4,990	5,544	5,933
1014	3,800	3,660	4,000	4,675	5,315	610	6,200	6,735
1015	3,160	3 173	3,563	4,117	4 716	3,394	3,946	6,558
1016	3,170	2,881	3,136	3,397	3 781	4,387	5,420	6,370
1017	3,320	3,233	3,500	4,029	4,586	3,025	5,953	6,558
1018	3,340	3,283	3,490	4,020	4,635	4,925	5,600	6,136
1019	3,000	3 100	3,215	3,821	4,236	4,597	5,320	6,139
1020	2,570	2,685	3,089	3 764	4,380	5,016	6,216	7,087
1021	3,580	3 776	4,055	5 139	5,909	5,945	6,158	6,098
1022	3,070	3,108	3 407	3,975	4,633	5,185	5,932	6,386
Incomplete Series—Males								
374	3,340	3,560	3 775	4,326	4,839	4,805	5 611	
302	3,690	3,530	3 699	4,440	5,085	5,713	6,360	
304	3,940	3 670	3 781	4,077				
308	3,300	3,227	3 467	4,144	4,688	5 052	3,871	
321	3,775	3,700	3,816	4,312	4 714	5 134	5 710	
323	4,530	4 700	4 782	5,428	5,853	6,191		
328	3,140	3 045	3,406	4,010	4,367	4,537	4,765	
347	3,150	3,080	3,244	3,654	4,115	4,638	4,865	
349	3,390	3,340	3,643	4 191	4,639	4,907	5,885	
360	3 490	3,330	3,541	4,218	4,864	5,376	6,224	
363	3,640	3,725	3,957	4,653	4,994	3,380	6,430	
364	3 110	3,263	3,525	4,380	5,207			
365	3,390	3 435	3,640	4,149	4,304	4,895		
368	3,610	3,605	3 730	3,987	4,384	4,566		
380	2,990	2,930	3,202	3,970	4,441	4,938		
384	3,040	2,904	3,090	3 423	3,490	3,561		
386	3,260	3,152	3,506	3,627				
389	3,300	3,246	3 478	4,130				
1004	3,230	3,058	3,283	4,020	4,522	4,831		
1005	4,125	4,271	4,502	3,060	4,418	4,875		
1006	3,860	3 764	4,012	4 406	5,672	5,896	6,314	
1008	3,560	3,537	3 747	4,361	4,854	5,363		
1009	3 770	3 913	4,071	4,573	4,884	5,156		
1011	3,395	3 175	3,368	4,010	5 117	5,496	6 468	
1023	3,640	3,900	3,713	4,223	4,494	4,904		
Complete Series—Females								
263	3,330	3 121	3,330	3 780	4,419	4,845	5,665	6,175
266	3,600	3,555	3,098	4,146	4,511	4,330	5,289	5,497
268	3,310	3 100	3,208	3,433	3,888	3,773	4 484	5,366

Appendix (cont)

Subject number	Birth	8 days	14 days	28 days	42 days	56 days	84 days	112 days
280	3 760	3,548	3 660	4 178	4 735	5 086	5,800	6,355
282	3 110	2,985	3 164	3,868	4,035	4,297	4 707	5,243
283	3,250	3 477	3 657	3 942	4 428	4 775	5,523	6 077
284	3 140	3,307	3,500	3 972	4,355	4,529	5 100	5 742
287	2,890	2,735	2,939	3,511	4 043	4,566	5,322	6,020
288	3 080	3,255	3,528	3,816	4 066	4,288	5 186	6,060
289	3,545	3 400	3,538	3,822	4,319	4 826	5 649	6,020
310	2,770	2,950	3,242	3 743	4 138	4,339	4 674	5,069
312	3,260	3,512	3 800	4 320	4,845	5 080	5,500	6 000
313	2,970	2,813	3 080	3 755	4,260	4 758	5,535	6,270
315	3,300	3,390	3 418	3 996	4 193	4 90..	5 996	6,954
317	3 310	3,286	3,548	4 185	4 945	5 428	5 781	6,307
330	3 060	3,200	3,302	3 790	4 1..8	4 40..	5,268	5,883
331	3 730	3,598	3 705	4 145	4,530	4 850	5,575	6 030
332	3 670	3 680	3,886	4 372	4 660	5 078	5 618	6,303
333	3 190	3,210	3 406	3 929	4 431	4 753	5,295	5 781
334	2,810	2,890	2,967	3,352	3,885	4,037	4,578	5,282
335	3 050	3,..60	3,369	3 910	4,392	4,811	5 424	5 700
337	3,350	3 405	3,580	4,230	4 671	5,218	6,005	6,653
339	2,840	2,746	2,845	3 485	3,950	4 405	5 170	5,590
350	2,860	2,676	3 041	3 634	3,970	4 194	4 871	5,349
352	2,500	2,689	2,783	3,299	3 816	4,276	5 124	5 740
353	3 000	3 053	3,346	4 162	4 692	5,363	6,265	7,349
354	3 900	3 863	3 930	4,250	4 635	4,950	5,335	5,885
355	3 170	3,231	3,268	3,820	4,360	4 672	5,322	5,934
358	2,820	2,650	2,990	3 650	4 175	4 690	5,305	5,959
370	3,080	3,220	3,520	3 969	4,330	4 668	5,218	5 659
371	3,560	3,525	3 650	3 765	3,930	4,243	4,885	5,545
372	3,520	3,396	3 605	4 060	4,300	4,560	5,020	5,550
373	3 020	..,890	3 136	3 641	4,236	4 728	5 441	5,844
375	3,820	3 750	4 116	4 684	5,299	5 704	6,313	6,993
377	3,290	3,230	3,522	3 881	4,283	4,522	5 038	4 981
379	3,560	3 493	3,577	3 935	4 427	4 691	5,398	5 952
390	3,570	3,355	3 62..	3 969	4,512	4 875	5,558	6 127
391	3 160	3 178	3 435	3 820	4,585	4,979	5,870	6 410
392	3,300	3 460	3 616	4 105	4 464	4 802	5 614	6,163
393	2,700	2,820	3 002	3,520	3,819	4 117	4 440	4,954
394	..,930	..,950	3 1..0	3 795	4,252	4 700	5 439	5 997
398	3 730	3 700	3 697	4,239	4 667	5 173	5 783	6 428
399	3 175	3,350	3,553	4 020	4,324	4,540	5 196	5 485
1100	3,380	3 421	3 650	4 154	4 654	5 161	5 779	6 448
1101	3,500	3,340	3 482	3 986	4 429	4 803	5,514	6,031
1102	3,320	3 157	3 445	4 188	4 759	5 064	5 687	5 987
Incomplete Series—Females								
262	2,930	3 035	3 142	3 607	4 045	4 457	5 158	
264	3,560	3 490	3 667	4,249	4 669	5 12..	5 674	
265	2,580	2,625	2,897	3,241	3,576			
267	3,220	3,210	3,510	4 031	4 603	4 927		
269	3,540	3,240	3,340	3 942	4,390	4 937	5,895	
281	3 200	3 425	3,801	4 731				
286	4 150	4 035	4,..84	4 660	5 034	5,244	5 735	
314	3 820	3 670	3 845	4 117				
316	3 180	3 180	3,268	3 619	3 956	4,373		
318	3 760	3,860	4 017	4 661	5 085	5 653		
319	3,230	3 128	3 110	3 010				
336	3,320	3 430	3 637	4,283	4 645	5,269		
351	3,210	3 005	3 130	3,390	3 700			
357	3,380	3,225	3 082	3 446	4 134	4 603	5 081	
359	3 160	3 118	3,397	3 961	4 442	4 85	5,289	
374	2,760	2,693	2,939	3 423	3 990	4 139	4 642	
376	2,530	2,513	2,766	3,289	3 832	4 050		
378	3 860	3 890	3 931	4 124	4 645			
396	3 980	3 939	4 005	4,392	4 621	4,887	5,364	
397	3 460	3 440	3 737	4 172	4,536			

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by

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In 1962, Bartter and associates (2) described two patients and briefly mentioned a third, who manifested a syndrome characterised by retarded growth, hypokalemic alkalosis, secondary hyperaldosteronism resistant to sodium loading and to plasma volume expansion, normal blood pressure and Pitressin resistant hyposthenuria. The circulating blood contained elevated concentrations of a pressor agent resembling angiotensin, and there was a significantly diminished response to infusion of angiotensin II. Kidney biopsies in two of the patients revealed hypertrophy and hyperplasia of the juxtaglomerular apparatuses (JGAs), and a partial adrenalectomy specimen in the first patient showed similar morphologic features of hyperfunction affecting the zona glomerulosa. The authors postulated resistance to the pressor action of angiotensin as the primary defect in the syndrome.

To date, at least 22 cases have been recorded (21 23 42), but our knowledge of the syndrome's pathogenesis has progressed little since its original description. Although the patients described below were originally investigated from 1954 to 1963 and were briefly recorded in two abstracts in the latter year (1 40), they are being reported in detail now because re-evaluation has brought to light certain features which may add to our understanding of this rare but very important entity.

MATERIALS AND METHODS

Sodium and potassium concentrations in plasma, cerebrospinal fluid (CSF) and urine were determined on a Baird Atomic KY 1 flame photometer and chloride by coulometric-amperometric titration (13). Calcium in plasma and CSF was estimated by EDTA titration (10 44). Inorganic phosphorus was determined in serum by the method of Horwitt (20), and magnesium by the titan yellow technique of Neill and Neely (30). Total plasma CO_2 was determined on the Micro Gasometer (26, 27). Blood pH was measured by means of the Astrup Micro Chain Electrode and that of urine by nitrazine paper. Urea nitrogen in blood and ammonia nitrogen in urine were measured by Conway's microdiffusion method (12). Blood sugar was determined by the methods of Somogyi (38) and Nelson (31) and urine sugar by Clinitest tablets (Ames and Co). CSF protein was precipitated by 3% sulphosalicylic acid and the resultant turbidity was read in a colorimeter. Urine protein was detected with Uristix (Ames and Co) and confirmed by the sulphosalicylic acid method of Bernhard and Scher (4).

Urinary 17-ketosteroids were estimated on 24-hour specimens as recommended by the Medical Research Council on Clinical Endocrinology (28). Amino acid content of urine was assessed on freshly voided specimens by ascending two-dimensional partition chromatography (14). Bio-Sciences Laboratory, California, estimated the urinary excretion of aldosterone by the method of Kliman and Peterson (24).

Special Tests. Studies on plasma and urine were carried out to determine the effects of (i) spironolactone administration and (ii) ammonium chloride loading on patient 1 while she was on a constant electrolyte intake of 35 mEq of Na and 65 mEq of K. Ammonium chloride loading was by a modification of the method of Elkinton et al (16). Angiotensin II (Ciba) was infused in patient 1 according to the technique of Bartter et al (2). Changes in both the systolic and diastolic blood pressures of the patient and one normal adult control were recorded and plotted in graph form, along with those obtained by Bartter and associates (2) for comparison (Fig. 1). Samples of kidney cortex of patients 1 and 2 were assayed for renin activity by an adaptation of the method of Goldblatt et al (18).

This investigation was supported by a United States Public Health Grant no A-6068 and an intramural grant from *The Research Institute The Hospital for* Sick Children, Toronto, Ontario, Canada.

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Table I *Birth Weights Age Weight and Length of Children on Admission and at Necropsy*

	Patient 1 Twin of Patient 2 (Died 1963)	Patient 2 Twin of Patient 1 (Died 1962)	Patient 3 Sib of Twins (Died 1959)	Patient 4 Unrelated (Died 1954)
Birth Weight in Kg.	3.07	2.91	3.26	Unknown
Age on Admission in mos.	6½	6½	4	3
Weight on Admission in Kg.	4.18	4.09	2.98	3.41
Length on Admission in cm.	59.5	58.5	—	—
Age at Death in mos.	13½	11	4	3½
Weight at Necropsy in Kg.	4.80	4.52	2.54	4.07
Length at Necropsy i cm.	65	62	59	63.5

slowed dramatically Both infants had shown a tendency to constipation from birth. At 3 months of age case 2 had an episode of respiratory infection, and at 4 1/2 months she had a febrile illness for one week following oral polio vaccine At 6 1/2 months of age both developed a febrile illness accompanied by anorexia and vomiting. This was considered to be a viral infection, since other members of the family were also affected. At that time a consultant pediatrician noted that the twins were very dystrophic with a degree of dehydration greater than could be explained by their current illness. They were admitted to the local hospital, where they were found to have severe alkalosis associated with low concentrations of serum sodium and chloride Case 1 failed to improve on intravenous therapy and was transferred to The Hospital for Sick Children. Case 2 was able to tolerate oral feedings but 3 days later she also was transferred for further investigation. Their mother had never noticed polyuria or polydypsia in either twin, but she noted that both had taken solid foods poorly

Physical examination revealed case 1 to be a pale, lethargic and moderately dehydrated, small, thin infant weighing 4.18 Kg. and measuring 59.5 cm. C. H Her mucous membranes were red and dry Case 2 appeared similar but was not clinically dehydrated she weighed 4.09 Kg. and measured 58.5 cm. C H (Table I) Constipated stool was palpable through her abdominal wall.

In both infants ECGs and blood pressures were normal, and the latter remained so throughout. An IVP showed that case 2 had normal kidneys and ureters but an enlarged bladder Laboratory tests revealed a marked degree of alkalosis, hypokalemia, hyponatremia and hypochloremia (Table III) Later hypomagnesemia was also demonstrated. While in this hospital, patient 2 continued to be constipated, but her twin sister (patient 1) had four episodes of diarrhea lasting 2 to 5 days in the 9th, 10th and 13th months of her life

Attempts to correct the electrolyte imbalance by means of oral and intravenous electrolyte solutions were unsuccessful The infants failed to gain weight they grew at most only about 1 cm. per month (*Table I*), and both had episodes of dehydration and collapse In each, gradual neurologic deterioration ensued, with drowsiness, lethargy convulsions and, finally loss of the sucking reflex. Case 2 developed *Ps. aeruginosa* pneumonia, septicemia and pyelonephritis in the last month of life and died at 11 months of age Case 1 died of Ps aeruginosa pneumonia at 13 1/2 months of age

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Age on Admission in mos.	6½	6½	4	3
Weight on Admission in Kg.	4.18	4.09	2.98	3.41
Length on Admission in cm.	59.5	58.5	—	—
Age at Death in mos.	13½	11	4	8½
Weight at Necropsy in Kg.	4.80	4.52	2.54	4.07
Length at Necropsy in cm.	65	62	59	63.5

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Table III. *Initial Serum Chemistry (In mEq /liter unless otherwise stated)*

	Normal Values	Patient 1	Patient	Patient 3	Patient 4
Sodium	135–145	130	137	132	136
Potassium	4–5.5	2 4	2.6	1 6	2.3
Chloride	98–108	68.2	69.5	72	82.8
CO_2 (total)	20–25	43.2	35.6	26.5	34 7
pH	7.35–7 45	7.54	7.36	7.3	7 45
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.
Calcium	9–11	10 1	10.3	—	12
Phosphorus	4–6	1.67	3.25	—	4.05
BUN	8–20	7.0	29 7	9 4	24.2

ran a fever up to 103 F He died at the age of 8 months and 3 weeks. He had been constipated throughout his life.

BIOCHEMICAL STUDIES ON PATIENTS 1 AND 2

Urine (Table II) Proteinuria was usually absent, or present only in trace amounts unless there happened to be an episode of dehydration or urinary infection Although the infants were never deprived of fluids for an extended period, they failed to concentrate urine even when severely dehydrated. Urine pH values were usually in the range of 7.0 to 7.5 There was no abnormality in the urine amino acid patterns. Microscopic findings in the urines were minimal, but during the terminal urinary infection of patient 2 her urine contained up to 50 pus cells and many red blood cells per high power field.

Serum. At 6 5 months of age findings in the local hospital were: patient 1 Hgb 10 6 gm./100 ml. Hct., 36.5% BUN 29.5 mg./100 ml. serum Na, 133 K 2.6 and Cl, 75 mEq /L, CO content, 4 mEq /L. In the case of patient 2, the BUN was 53 mg./100 ml. serum Na, 131 Cl, 79 CO content, 79 mEq /L. Ca, 11 mg./100 ml., and P 3.5 mg./100 ml. Values obtained after admission to this hospital are shown in Table III

After correction of the dehydration the BUN values remained within normal limits. Rehydration however was accompanied by falling serum sodium levels. With the exception of a short period during which regular injections of magnesium sulfate (v.i.) were given both infants showed persistently low levels of serum sodium, potassium and chloride also elevated pH and CO_2 content. Intramuscular $MgSO_4$ soon led to, or coincided with, severe dehydration and on rehydration, there was a precipitous fall in electrolyte values and edema developed. Oral potassium supplements coincided with a further decline in the already abnormally low serum sodium levels In an attempt to prolong life it was necessary to give as much as 3% sodium chloride solution intermittently in amounts up to 100 ml and up to 12 mEq /Kg./day of potassium intravenously but even these failed to elevate the serum Na and K to normal values

Effect of Intramuscular Magnesium Sulphate Over a 48 hour period each twin received 0 8 ml of 50% MgSO solution intramuscularly every 12 hours. On the second day of this regimen plasma sodium concentration had risen to 151 mEq /L. in patient 1 and to 156 mEq /L. in patient 2. On the day following cessation of this therapy the values were 144.5 and 134 mEq /L., and 48 hours after the last $MgSO_4$ injection they had fallen to 124.5 and 125 mEq /L. in patients 1 and 2, respectively Plasma chloride levels paralleled those of sodium, reaching peaks of 116 and 115 mEq /L. in patients 1 and 2 on the second day of parenteral magnesium, when total plasma CO had declined to 26 4 and 26.9 mEq /L.,

Table II *Summary of Urinalyses—4 patients*

	Patient 1	Patient 2	Patient 3	Patient 4
Protein	Neg to 2+	Neg to +	Neg to +	Neg
Glucose	Neg	Neg	Neg to 4+	Neg
pH	6.69–7 71	6.3–7 08	Alkaline	7.3–7.5
Specific Gravity	1.005–1.011	1.003–1 015	1 001–1 006	—

the third month they noted a complete failure to gain weight. At the beginning of the 4th month of age she was admitted to the local hospital where she was noted to be wasted and the BUN on two occasions was recorded as 87 and 64 mg./100 ml Her urine contained 1+albumin 3–4 pus cells and 3–4 red blood cells/H P field An IVP revealed poor renal concentrating power She was then transferred to this hospital

On admission she had a greyish pallor was dehydrated and wasted being some 300 gm less than her birth weight (Table I) One ear drum appeared dull There was severe hypokalemia and hypochloremia (Table III) Since she exhibited glycosuria (Table II) blood and urine sugars were correlated on three successive days when the blood sugar was 279 102 and 112 mg./100 ml the urine sugar was 3 plus negative and 1 plus respectively

Urine amino acid chromatograms were normal Pitressin failed to affect the output of large volumes of dilute urine the highest specific gravity reached was 1 006 Constipation was always present, both prior to and during her entire hospitalization She was given potassium supplements by mouth as well as continuous intravenous infusions of both sodium and potassium Achromycin was given for otitis media. However she deteriorated progressively had a general convulsion on the 5th hospital day and died on the 7th day after admission

Case 4 This male infant, the product of incest between a father and his 19 year-old daughter was born November 1 1953 The birth weight was not recorded, but he was admitted to the local hospital at 3 weeks of age because of failure to gain he then weighed 8 lbs., and despite intensive care he failed to gain weight during the subsequent 2 ½ months at that hospital At 14 weeks of age he was transferred to this hospital because of failure to thrive and severe muscle weakness.

On examination, he was bright and alert but was feeble, with poor muscle tone, and was unable to hold his head up There was little if any subcutaneous fat and he appeared dehydrated. He weighed 7 lbs 8 ozs. He fed poorly lost weight and became increasingly dehydrated on a fluid intake of 20 ozs /day At 18 weeks of age his serum electrolytes were: K, 2 8 Na, 131 and Cl, 65.5 mEq/L. Despite oral and IV fluids, including up to 1200 ml of 0.3% KCl per day he continued to lose weight and fluids. From age 4 to 8 months his serum K ranged from 2 3 to 3 0 mEq /L. Na, from 121 to 136 mEq /L and Cl from 64.5 to 82 8 mEq /L At age 7 ½ months his blood pH was 7 45 and CO c p 80 vols % Balance studies were attempted but because the patient vomited the gavaged fluid the test was not completed By intravenous route on June 22 to June 25th. the child received 90 cc of 0 3% KCl solution containing a total of about 4 mEq of K On June 23 he excreted 25 mEq of K. That is, he appeared to be excreting more K than he was receiving. Urinary 17 ketosteroid excretion was 0 3 and 0 2 mg. day on two occasions. Urinary amino acid chromatograms were normal, and there was never any sugar in the urine Serum Ca and P were normal BUN readings were 19 8 24 2, 33 1 and 9 7 mg./100 ml at ages 4 5 ½ 6 and 7 months, respectively Hemoglobin ranged from 11 4 to 13 1 gm 100 ml but fell to 9 4 gm 10 days prior to death. In the last 8 weeks of life he

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Potassium	4–5.5	2.4	2.6	1.6	2.3
Chloride	98–108	68.2	69.5	72	82.8
CO_2 (total)	20–25	43.2	35.6	26.5	34 7
pH	7.35–7 45	7.54	7.56	7.3	7 45
	mg./100 ml.	mg./100 ml.	mg./100 ml	mg./100 ml.	mg./100 ml.
Calcium	9–11	10.1	10 3	—	12
Phosphorus	4–6	1.67	3.25	—	4.05
BUN	8–20	7 0	29 7	9 4	24..

ran a fever up to 103 F He died at the age of 8 months and 3 weeks. He had been constipated *throughout his* life.

BIOCHEMICAL STUDIES ON PATIENTS 1 AND 2

Urine (Table II) Proteinuria was usually absent, or present only in trace amounts unless there happened to be an episode of dehydration or urinary infection Although the infants were never deprived of fluids for an extended period, they failed to concentrate urine even when severely dehydrated. Urine pH values were usually in the range of 7.0 to 7.5 There was no abnormality in the urine amino acid patterns. Microscopic findings in the urines were minimal, but during the terminal urinary infection of patient 2 her urine contained up to 50 pus cells and many red blood cells per high power field

Serum. At 6.5 months of age findings in the local hospital were patient 1 Hgb 10 6 gm./100 ml. Hct. 36.5% BUN 29.5 mg./100 ml. serum Na, 133 K 2.6, and Cl, 75 mEq /L. CO_2 content, 47 mEq /L. In the case of patient 2, the BUN was 53 mg./100 ml serum Na, 131 Cl, 79 CO content, 79 mEq /L. Ca, 11 mg./100 ml and P 3.5 mg / 100 ml. Values obtained after admission to this hospital are shown in Table III.

After correction of the dehydration the BUN values remained within normal limits. Rehydration however was accompanied by falling serum sodium levels. With the exception of a short period during which regular injections of magnesium sulfate (v.i.) were given both infants showed persistently low levels of serum sodium, potassium and chloride, also elevated pH and CO_2 content. Intramuscular $MgSO_4$ soon led to, or coincided with, severe dehydration and on rehydration, there was a precipitous fall in electrolyte values and edema developed. Oral potassium supplements coincided with a further decline in the already abnormally low serum sodium levels. *In an attempt* to prolong life it was necessary to give as much as 3% sodium chloride solution intermittently in amounts up to 100 ml and up to 12 mEq /Kg./day of potassium intravenously but even these failed to elevate the serum Na and K to normal values.

Effect of Intramuscular Magnesium Sulphate Over a 48 hour period each twin received 0 8 ml. of 50% MgSO solution intramuscularly every 12 hours. On the second day of this regimen plasma sodium concentration had risen to 151 mEq /L. In patient 1 and to 156 mEq /L. in patient 2 On the day following cessation of this therapy the values were 144.5 and 134 mEq /L., and 48 hours after the last MgSO injection they had fallen to 124.5 and 125 mEq /L. In patients 1 and 2, respectively Plasma chloride levels paralleled those of sodium, reaching peaks of 116 and 115 mEq / L. In patients 1 and 2 on the second day of parenteral magnesium, when total plasma CO had declined to 26 4 and 26 9 mEq /L

Table II *Summary of Urinalyses—4 patients*

	Patient 1	Patient 2	Patient 3	Patient 4
Protein	Neg to 2+	Neg to +	Neg to +	Neg
Glucose	Neg	Neg	Neg to 4+	Neg
pH	6.69–7 71	6.3–7.08	Alkaline	7.3–7.5
Specific Gravity	1 005–1.011	1 003–1.015	1 001–1.006	—

the third month they noted a complete failure to gain weight. At the beginning of the 4th month of age she was admitted to the local hospital where she was noted to be wasted and the BUN on two occasions was recorded as 87 and 64 mg./100 ml Her urine contained 1+albumin, 3–4 pus cells and 3–4 red blood cells/H P field. An IVP revealed poor renal concentrating power She was then transferred to this hospital

On admission she had a greyish pallor was dehydrated and wasted being some 300 gm. less than her birth weight (Table I) One ear drum appeared dull There was severe hypokalemia and hypochloremia (Table III) Since she exhibited glycosuria (Table II) blood and urine sugars were correlated on three successive days when the blood sugar was 279 102 and 112 mg./100 ml., the urine sugar was 3 plus, negative and 1 plus, respectively

Urine amino acid chromatograms were normal Pitressin failed to affect the output of large volumes of dilute urine the highest specific gravity reached was 1 006 Constipation was always present, both prior to and during her entire hospitalization She was given potassium supplements by mouth as well as continuous intravenous infusions of both sodium and potassium Achromycin was given for otitis media. However she deteriorated progressively had a general convulsion on the 5th hospital day and died on the 7th day after admission

Case 4 This male infant, the product of incest between a father and his 19 year-old daughter was born November 1 1953 The birth weight was not recorded, but he was admitted to the local hospital at 3 weeks of age because of failure to gain he then weighed 8 lbs and despite intensive care he failed to gain weight during the subsequent 2 1/2 months at that hospital At 14 weeks of age he was transferred to this hospital because of failure to thrive and severe muscle weakness

On examination, he was bright and alert but was feeble with poor muscle tone and was unable to hold his head up There was little if any subcutaneous fat and he appeared dehydrated He weighed 7 lbs 8 ozs He fed poorly lost weight and became increasingly dehydrated on a fluid intake of 20 ozs./day At 18 weeks of age his serum electrolytes were K, 2 8 Na, 131 and Cl, 65.5 mEq/L. Despite oral and IV fluids, including up to 1200 ml of 0.3% KCl per day he continued to lose weight and fluids. From age 4 to 8 months his serum K ranged from 2 3 to 3 0 mEq /L. Na, from 121 to 136 mEq /L., and Cl from 64.5 to 82 8 mEq /L At age 7 1/2 months his blood pH was 7 45 and CO_2 c p 80 vols % Balance studies were attempted but because the patient vomited the gavaged fluid the test was not completed By intravenous route on June 22 to June 25th the child received 90 cc of 0.3% KCl solution containing a total of about 4 mEq of K. On June 23 he excreted 25 mEq of K. That is he appeared to be excreting more K than he was receiving. Urinary 17 ketosteroid excretion was 0 3 and 0 2 mg./day on two occasions Urinary amino acid chromatograms were normal, and there was never any sugar in the urine Serum Ca and P were normal. BUN readings were 19 8, 24 2 33 1 and 9 7 mg./100 ml at ages 4 5 1/2 6 and 7 months, respectively Hemoglobin ranged from 11 4 to 13 1 gm 100 ml but fell to 9 4 gm. 10 days prior to death In the last 8 weeks of life he

Table VI. *Patient 1 Serum Chemistry During Ammonium Chloride Loading (In mEq./liter unless, otherwise stated)*

	Control	Day 2	Day 3	Day 4	Day 5
Sodium	128	123.5	130.5	128.0	126.5
Potassium	2.9	3.7	3.3	2.55	2.55
Chloride	78.0	87.0	84.0	89.5	81.0
Magnesium	1.05	1.48	1.52	1.62	1.16
Carbon Dioxide (total)	36.0	21.7	33.8	28.9	26.5
pH	7.60	7.51	7.58	7.54	7.60
BUN	9.4 mg./100 ml.	—	—	10.3 mg./100 ml.	—

pairment of the ability to excrete ammonium ions, but the urine pH remained unchanged and did not fall below neutrality. There was no evidence of any persistent effect on cation excretion.

Cerebrospinal Fluid. Patient 2 had a lumbar puncture during the latter part of her hospitalization. The results (Table VIII) indicate low levels of sodium and chloride but the concentrations of potassium and calcium were normal. Regrettably simultaneous determinations of serum electrolytes were not carried out.

SPECIAL INVESTIGATIONS

Aldosterone. Urine excretion values for aldosterone were 28 μg./24 hours for patient 1 and 10 μg./24 hours for patient 2, when each was receiving 3 gm sodium chloride supplement per day. These values are significantly elevated (32) especially in the case of patient 1.

Angiotensin and Renin. In both infants repeated blood pressure recordings gave values of 95/55 or less. Only patient 1 was well enough to permit angiotensin infusion studies. This infant proved to be extremely resistant to large doses of angiotensin II, showing even less response than Bartter's patients (2). When the dose of angiotensin was raised to 1 μg/Kg of body weight, there was a rise of only 10 to 12 mm. Hg. in the systolic and 22 mm. Hg. in the diastolic pressures. A normal adult receiving the same doses of angiotensin as given to this infant showed marked increases of blood pressure. Plasma renin and angiotensin were not determined in either infant, but assays of renin in the kidney cortices obtained at necropsy from both patients gave values 50 to 200 times those obtained in normal adult kidney cortex.

GROSS NECROPSY FINDINGS

Case 1. Necropsy was begun within 30 minutes of death and revealed an underdeveloped, undernourished female infant, 4800 gm. and 65 cm. C.H. Both lungs were affected by Ps. aeruginosa bronchopneumonia. The kidneys (R., 52 L., 50 gm.) presented smooth, pale

Table VII. *Patient 1 Urine Chemistry During Ammonium Chloride Loading (In mEq./day)*

	Control (24 hours)	Second (24 hours)	Third (24 hours)	Fifth (24 hours)
Sodium	34.3	50.5	42.5	37.4
Potassium	59.4	69.9	54.2	44.2
Chloride	83.7	100.9	94.8	94.3
Carbon Dioxide (total)	15.7	—	7.6	10.6
pH	7.13	7.10	7.10	—
Titratable acidity	4.2	3.19	3.49	3.31
Ammonia N	18.6	28.6	34.4	18.8
24 hour Volume ml	837	885	780	890

Table IV *Patient 1 Serum Chemistry During Spironolactone Administration (In mEq /liter unless otherwise stated)*

	Pre Spironolactone Control	Day 3	Day 6	Day 9
Sodium	131.5	124.5	128.0	125.5
Potassium	2.4	2.9	2.4	2.15
Chloride	69 0	74 5	72.0	76.0
Magnesium	1.26	1 01	—	—
Carbon Dioxide (total)	33.2	34 4	34 4	26.6
pH	7 58	7.51	7 54	7.51
	mg./100 ml.	mg./100 ml	mg./100 ml	mg./100 ml.
Calcium	8.7	9..	9.2	—
Phosphorus	—	4 7	1 88	—
BUN	10 8	10	8 9	—

respectively Serum calcium became considerably elevated being recorded as more than 15 mg./100 ml in patient 1 and 12 4 mg /100 ml in patient 2 on the day following cessation of intramuscular $MgSO_4$ Plasma potassium reached peaks of 4 6 and 5 0 mEq /L. in patients 1 and 2 respectively 1 1/2 and 4 days following cessation of $MgSO_4$ injections

Serum Magnesium This was studied because convulsions and neurologic deterioration continued despite adequate calcium intake. Before magnesium therapy was commenced serum Mg concentrations in patients 1 and 2 were 0 77 and 0 79 mEq /L. (normal range in our laboratory 1 5 to 1 9 mEq /L.) Ingestion of milk of magnesia (2 ml., 1 to 3 times per day) had little or no effect on serum levels of this cation and although daily intravenous infusions of 8 mEq of $MgCl_2$ raised these values temporarily they had always fallen to low levels again within 16 hours after the termination of each infusion. Intramuscular injections of $MgSO_4$ proved unsatisfactory both because of the severe local tissue damage and the dehydration which they caused

Effect of Spironolactone Spironolactone was given orally to patient 1 in a dose of 25 mg. every 6 hours for a period of nine days, during which her electrolyte intake was constant. As shown in Table IV the plasma concentrations of sodium, potassium and magnesium were not significantly altered during the administration of this drug, nor did the BUN or plasma pH show any change of consequence Plasma CO_2 however showed a reduction on day 9 Urine values (Table V) suggested some retention of sodium during spironolactone administration.

Effect of Ammonium Chloride Loading As shown in Table VI, ammonium chloride loading (0 059 gm /Kg q8h × 5 days) in the case of patient 1 caused no significant change in serum sodium or chloride On the third day of loading the plasma potassium rose to 5.5 mEq /L but on the other days it remained within the narrower range of 2 55 to 3 7 mEq L. The CO_2 content decreased slightly but the plasma pH on day 5 was the same as the pre loading baseline value i. e 7 60 Values obtained from 24-hour urine specimens during ammonium chloride loading are set out in Table VII Evidently there was no im-

Table V *Patient 1 Effect of Spironolactone on Urine Chemistry (In mEq /liter)*

	Control (24 hrs)	Third (24 hrs)	Ninth (24 hrs)
Sodium	52	40	43
Potassium	71	72	83
Chloride	111	1?4	116
pH	7 54	6.69	7 17
4 hour Volume ml.	948	887	805

Table VI. *Patient 1 Serum Chemistry During Ammonium Chloride Loading (In mEq./liter unless otherwise stated)*

	Control	Day 2	Day 3	Day 4	Day 5
Sodium	128	123.5	130.5	128.0	126.5
Potassium	2.9	3 7	5.3	2.55	2.55
Chloride	78.0	87.0	84.0	89.5	81.0
Magnesium	1 05	1.48	1.52	1 62	1 16
Carbon Dioxide (total)	36.0	21 7	33.8	28.9	26.5
pH	7.60	7.51	7.58	7.54	7.60
BUN	9 4 mg./100 ml.	—	—	10.3 mg./100 ml.	—

pairment of the ability to excrete ammonium ions, but the urine pH remained unchanged and did not fall below neutrality There was no evidence of any persistent effect on cation excretion.

Cerebrospinal Fluid Patient 2 had a lumbar puncture during the latter part of her hospitalization. The results (Table VIII) indicate low levels of sodium and chloride but the concentrations of potassium and calcium were normal. Regrettably simultaneous determinations of serum electrolytes were not carried out.

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Table VII *Patient 1 Urine Chemistry During Ammonium Chloride Loading (In mEq./day)*

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Sodium	34.3	30.5	42.5	37 4
Potassium	59 4	69 9	54.2	48.2
Chloride	83 7	100 9	94.8	94.3
Carbon Dioxide (total)	15.7	—	7.6	10 6
pH	7 13	7 10	7 10	—
Titratable acidity	4.2	3.19	3.49	3.31
Ammonia N	18.6	28.6	34.4	18 8
24 hour Volume ml	837	885	780	890

Table VIII *Patient 2 Chemistry of Cerebrospinal Fluid (In mEq /liter unless otherwise stated)*

	Normal	Case 2
Sodium	142–150	128.5
Potassium	2.3–3.2	3 4
Chloride	120–130	98.0
Protein	20–40 mg/100 ml	26.0 mg/100 ml

tan capsular surfaces and pale cut surfaces, with poor demarcation of the cortico-medullary junctions The brain (405 gm.) was markedly atrophic, being separated from the vault of the skull by a 1.5 cm. space The leptomeninges were thickened, gelatinous and yellowish-tan in color An organizing subdural hematoma (1.5–2 ozs.) was present over the left lateral occipito-parietal region Cortical atrophy and diffuse ventricular dilatation were evident on gross sectioning. The basal ganglia, midbrain pons medulla, cerebellum and spinal cord were grossly normal.

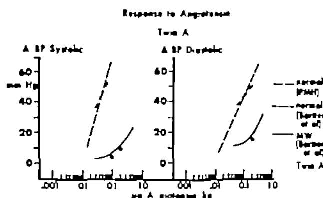


Fig 1 Graphic representation of blood pressure response in patient 1 (Twin A) to angiotensin II infusion. The continuous line curve is plotted from the values obtained by Bartter et al. (1) in their second patient, M W

Fig 2 Dilatation and vacuolation of convoluted tubules of kidney from patient 3 Hematoxylin-eosin ×460

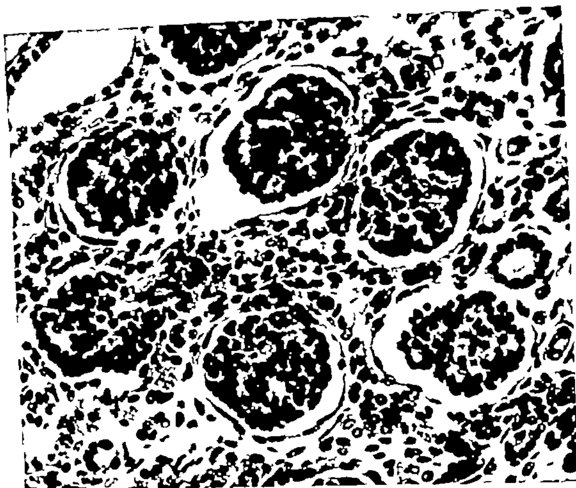


Fig. 3 A cluster of six immature glomeruli in the outer renal cortex of patient 2. One shows hyperplastic (but not hypertrophic) JGA in longitudinal section, Hematoxylin-eosin. 460.

Case 2 Necropsy was begun 30 minutes after death and showed an underdeveloped, undernourished female infant, 4520 gm. and 62 cm. C.H There was bilateral Ps. aeruginosa bronchopneumonia. Both kidneys were enlarged (R., 58 L., 55 gm.) The capsular surfaces were smooth the cut surfaces revealed diffuse pallor with poor delineation of the cortico-medullary junction in most areas. The left kidney showed several small foci of suppuration, especially in the medulla. The brain (480 gm.) was firm and symmetrically atrophic, with diffuse ventricular dilatation of moderate degree and cortical atrophy evident on gross sectioning.

Case 3 Necropsy was undertaken 14 hours after death and revealed a marantic female infant (2538 gm.) measuring 59 cm. C.H. The kidneys (R., 27 L., 24 gm.) were pale soft and appeared swollen. Suppurative pyelonephritis involved the lower two-thirds of the left kidney The remainder of this kidney and the entire right kidney showed pale tan cut surfaces but were otherwise unremarkable The brain (499 gm.) appeared grossly normal.

Case 4 Unfortunately because of difficulty in obtaining legal consent necropsy was not done until 110 hours after death. In the interval the body was kept at 4 C. Examination revealed a small (4068 gm.) dystrophic male infant. There was slight internal hydrocephalus but in the gross the other organs were

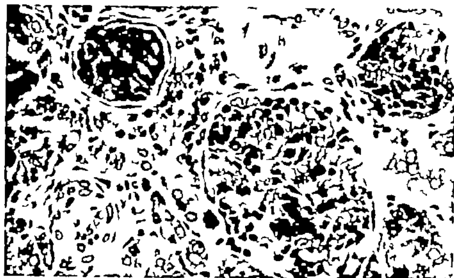


Fig 4 Thin, Epon-embedded section of renal cortex from patient 2, showing one large and two small glomeruli. The large glomerulus appears histologically mature The small glomeruli appear immature with few capillaries but numerous cuboidal epithelial cells. Note medial hypertrophy of artery in upper right corner Toluidine blue stain. 420

described as being unremarkable Death was attributed to electrolyte imbalance

HISTOPATHOLOGY
(Light microscopy)

Kidneys Scattered calcific deposits were seen both within and external to the medullary tubules Focal acute pyelonephritis was seen in the left kidney of case 2 and acute suppurative pyelonephritis involved the lower two-thirds of the left kidney of case 3 Dilatation of the convoluted tubules with vacuolation of the lining epithelial cells was prominent focally in case 3 (fig 2) but these changes were slight in the other cases Occasional proteinaceous casts were seen in all four cases.

A striking feature was the presence of two populations of glomeruli one of normal size the other hypoplastic Most of the latter measured less than half the size of the larger glomeruli and they showed the morphologic features of immature neonatal or fetal glomeruli (Figs 3 and 4) The peripheries of their closely set, rather solid and relatively avascular tufts were covered by many closely apposed small dark cuboidal cells with very little cytoplasm The majority of these small glomeruli appeared to be non functional (or minimally so) and their associated tubules seemed to be equally small crowded and inactive In distribution also these hypoplastic glomeruli resembled the fetal type 90 per cent were located in the outer cortices The proportion of all glomeruli which were immature ranged from 55 to 35 per cent and was greater in the younger patients (Table IX)

Of the large or mature glomeruli, from 47 to 88 per cent displayed hypertrophy and hyperplasia of their JGAs, the higher proportions being found in the older patients (Table IX) More often than not the hyperplastic JG-cells appeared to bulge into the root of the glomerulus, where they were continuous with and difficult to distinguish from what seemed to be hyperplastic and hyperchromatic mesangial cells (Fig. 5) The maculae densae of glomeruli having hypertrophied JGAs were very prominent, with crowded nuclei on the JGA side of their walls Here the cells of the maculae densae were cuboidal to low-columnar and had very little cytoplasm on the luminal aspects of their nuclei (Fig. 6) In many but not all instances Gomori s methenamine silver and Gordon and Sweets stains revealed that the macula densa cells rested on a well-developed basement membrane and in H and E stained sections, a slit like space could occasionally be seen separating the JG cell mass from the macula densa (Fig. 5) Bowie s stain showed abundant dark-purple granules in many of the hypertrophied JG cells (Fig. 7) but this granulation did not extend for more than a few microns into the stalks of the glo-

Table IX. *Morphological Evaluation of Glomeruli and Juxtaglomerular Apparatuses in Four Patients with Bartter's Syndrome*

1 Case No. Age at death
2 Hypoplastic glomeruli as percentage of total counted (Parentheses)
3 Large glomeruli having hypertrophic JGA, as percentage of total counted (Parentheses)
4 Small glomeruli having hyperplastic JGA, as percentage of those counted (Parentheses)
5 Means of greatest and least diameters[a] of 30 largest JGA in microns; ranges in parentheses
6 Mean diameter[b] of largest glomeruli in microns range and number counted in parentheses
7 Mean diameter[b] of smallest immature glomeruli in microns, range and number counted in parentheses

1	2	3	4	5	6	7
Case 1 14 mos 20 controls[c] 11 to 14 mos	35.0 (1500) 2.4 range 0 to 7	88 (230)	40 (200)	101 55 (68 40 to 110 95)	155 (136–190) (33)	50 (34–68) (33)
Case 2 11 mos 20 controls[c] 11 to 14 mos	42 (2286) 2.4 range 0 to 7	76 (168)	35 (200)	77 42 (52 34 to 109 68)	157 (123–190) (35)	55 (35–69) (35)
Case 3 4 mos 15 controls[c] 4 to 5 mos	55 (1200) 14.4 range 8 to 35	47 (133)	22 (105)	61 37 (35 27 to 100 55)	151 (130–170) (24)	51 (35–70) (24)
Case 4 8 mos 16 controls[c] 8 to 9 mos	47 (2684) 8.0 range 2.6 to 15	73 (240)	31 (200)	70 43 (54 34 to 100 61)	152 (125–170) (30)	53 (36–72) (30)

Cases 1, 2 and 3 were siblings and unrelated to M.B., 1 and 2 were twins.
Only those glomeruli were counted or measured in which the vascular pole was clearly seen.
In each JGA the diameters measured were approximately at right angles to each other
[c] In each control 300 glomeruli were counted in continuous radial sweeps from cortex to medulla.

meruli. The size of the hypertrophic JGAs appeared to increase with age (Table IX).

Because of the crowded structure of the immature glomeruli, it was usually difficult to judge whether their JGAs were hyperplastic. Between 20 and 40 per cent of these glomeruli were thought to show some hyperplasia of their JGAs, but for the reason just stated these figures are not advanced as accurate ones. In any case, hyperplastic JGAs of immature glomeruli were quite dissimilar to the hypertrophic JGAs of mature glomeruli: the former showed only an increase in cell numbers, the individual cells being small and tightly packed. Rarely one encountered an immature glomerulus which displayed some hypertrophy as well as hyperplasia of its JG cells (Fig. 8).

In none of the glomeruli, small or large, in any of the four patients were adhesions seen between the tufts and Bowman's capsule. Furthermore, of the some 9 700 glomeruli examined in preparation of Table IX, none were fully sclerosed, and only 29 were partly sclerosed, viz., 5 mature glomeruli in case 1, 3 mature glomeruli each in cases 2 and 4, the remainder being partly sclerosed hypoplastic glomeruli distributed more or less evenly between the 4 cases.

Another striking morphologic feature of the kidneys was hyperplastic thickening of the walls of arteries measuring up to 150 μ O.D. By far the more significant factor here was medial smooth muscle hyperplasia (Figs. 4 and 9) but intimal cells were also very prominent in the smaller arterioles. This medial arterial thickening was most prominent in patients 1 and 2. It was less marked in case 4 and was least (but still significant) in case 3. While arterial thickening was present to some degree in many other tissues from cases 1 and 2, it never amounted to more than 30% of the

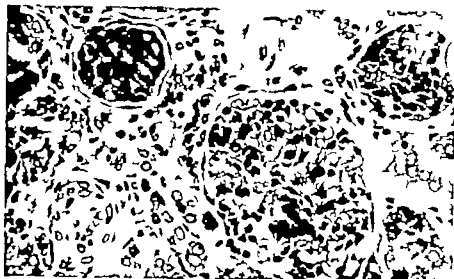


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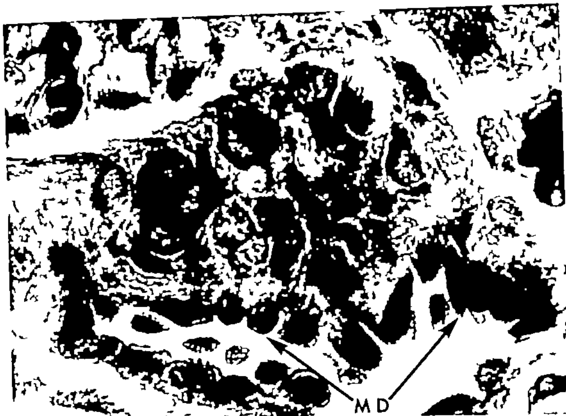


Fig. 7 JG cells from patient 1 showing clusters of granules near to and overlying the nuclei.
Bowie's stain, 1840 MD = macula densa.

outer cortex. In the two older patients the cortical cells here were uniformly vacuolated and enlarged (Fig. 10) and they stained intensely with oil red O in frozen sections. In the younger patients the hypertrophied glomerulosa zones were more obvious and their outer cells appeared more compact and less vacuolated (Fig. 11)

Pancreatic Islets Rather marked hyperplasia of the islets of Langerhans was present in both patients 1 and 2. In case 4 there was judged to be a slight but definite increase in islet tissue, which in case 3 appeared normal.

Pituitary Glands No abnormalities were detected in sections stained by hematoxylin-eosin, trichrome or Ezrin-Wilson (17) methods.

Parathyroid Glands In only one of the four patients (case 2) were these seen in sections. They appeared normal in this instance

Brains No special studies were conducted. In both patients 1 and 2 there was a diffuse moderate loss of cortical neurons, and there was a proportionate reduction of subcortical myelin, with some increase in glial cells in both of these areas. Similar but very much milder changes were seen in case 4 but the brain of case 3 appeared normal.

Electron Microscopic Findings

The small glomeruli appeared immature with incompletely developed capillary networks and the cuboidal epithelial cells already mentioned under light microscopy These immature podocytes characteristically contained scanty cytoplasmic organelles, and their foot processes were either absent or fused and replaced by a continuous sheet of cytoplasm (Fig. 12) The surface of the epithelial cytoplasmic sheet



Fig 5 A relatively mature glomerulus from case 1 showing hypertrophied JGA bulging into the stalk of the glomerulus, where the JG cells appear to be continuous with the hyperplastic and hyperchromatic mesangial cells. The bases of the macula densa cells appear to be separated from the JG cell mass by a narrow space or cleft. Note also the thick-walled arteriole toward lower left. Hematoxylin-eosin. × 460

severity seen in the kidneys it was present to some degree in the suprarenal capsules, submucosa of the small intestines, liver pancreas, voluntary muscle and brain. In patients 3 and 4 arterial thickening was equivocal or absent outside of the kidneys.

Adrenal Glands In all four cases there were significant hypertrophy and hyperplasia of the

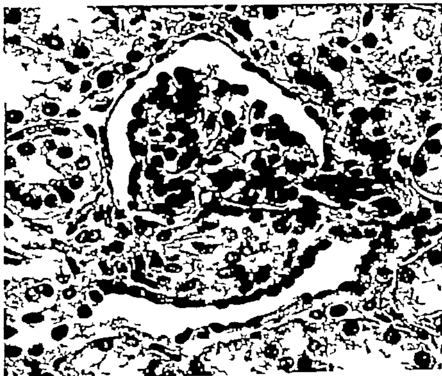


Fig 6 Hypertrophied JGA from case 2, showing crowded nuclei of macula densa Note that there is very little cytoplasm on the luminal aspects of these nuclei. Hematoxylin-eosin. 460.

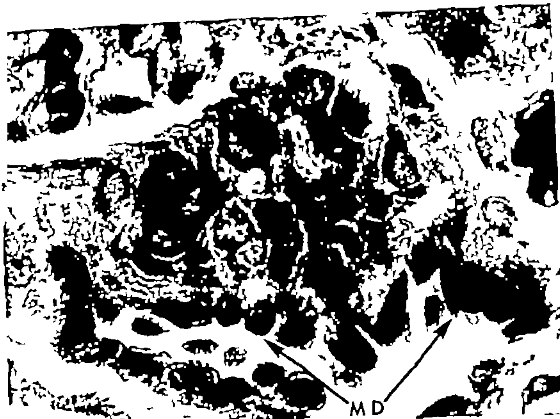


Fig 7 JG cells from patient 1 showing clusters of granules near to and overlying the nuclei. Bowie stain, 1840. MD = macula densa.

outer cortex. In the two older patients the cortical cells here were uniformly vacuolated and enlarged (Fig. 10) and they stained intensely with oil red O in frozen sections. In the younger patients the hypertrophied glomerulosa zones were more obvious and their outer cells appeared more compact and less vacuolated (Fig. 11)

Pancreatic Islets. Rather marked hyperplasia of the islets of Langerhans was present in both patients 1 and 2. In case 4 there was judged to be a slight but definite increase in islet tissue which in case 3 appeared normal

Pituitary Glands. No abnormalities were detected in sections stained by hematoxylin-eosin, trichrome or Ezrin-Wilson (17) methods.

Parathyroid Glands In only one of the four patients (case ?) were these seen in sections. They appeared normal in this instance.

Brains No special studies were conducted. In both patients 1 and 2 there was a diffuse moderate loss of cortical neurons, and there was a proportionate reduction of subcortical myelin, with some increase in glial cells in both of these areas. Similar but very much milder changes were seen in case 4 but the brain of case 3 appeared normal.

Electron Microscopic Findings

The small glomeruli appeared immature wit incompletely developed capillary networks an the cuboidal epithelial cells already mentione under light microscopy These immature podocytes characteristically contained scanty cytoplasmic organelles, and their foot processe were either absent or fused and replaced by a continuous sheet of cytoplasm (Fig. 12) Th surface of the epithelial cytoplasmic shee

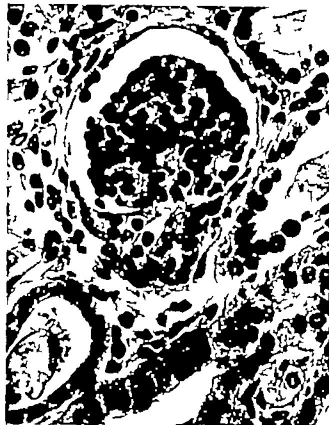


Fig 8 An immature glomerulus from patient 2, showing hyperplasia and some hypertrophy of its JG cells. Note the unexpanded, avascular appearance of the glomerulus and its covering of crowded, small cuboidal epithelial cells also the protein casts in three tubules. Hematoxylin-eosin. 575

which faced the urinary space often showed many slender cytoplasmic projections, and in places these appeared to connect adjacent areas of podocytic cytoplasm (Fig. 13) Large glomeruli showed qualitatively similar features with the exception that their capillaries appeared well developed In both small and large glomeruli the mesangial regions were often focally broadened

In the JG cells there were numerous dense granules limited by single membranes, and large cisternae of the rough surfaced endoplasmic reticulum were frequently associated with prominent Golgi complexes Abundant, amorphous, basement membrane-like material was present between the juxtaglomerular cells

Both proximal and distal tubules often revealed many cytoplasmic bodies and profiles of dilated rough endoplasmic reticulum At the bases of the tubular cells the juxtaposed cytoplasmic compartments were frequently separated by large extracellular spaces In addition, the basement membranes of the tubular cells often revealed splitting and reduplication.

Fluorescence Microscopy Sections of kidneys from both patients 1 and 2 when exposed to conjugated canine anti pig renin serum, exhibited intense fluorescent staining of granules within the juxtaglomerular cells Direct blocking tests in which the conjugated antiserum was first exposed to pig renin abolished about 85 % of this staining

Kidney Enzymes These were investigated in material from patient 1 The proximal portions of the tubules stained only faintly for alkaline phosphatase and $NADH_2$-tetrazolium reductase These results were interpreted as non

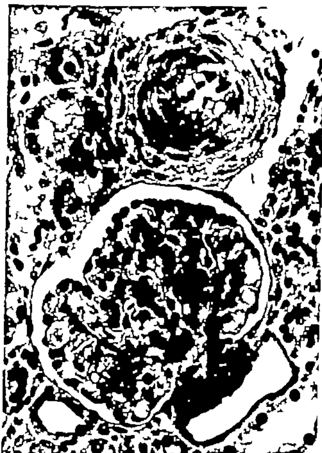


Fig 9 Hyperplastic arterial thickening in kidney of patient 1 There is an obvious increase in medial smooth muscle cells, and the endothelial cells are swollen and hydropic. Below the artery is a mature glomerulus with its associated macula densa and portion of its hypertrophied JGA Hematoxylin-eosin 460.

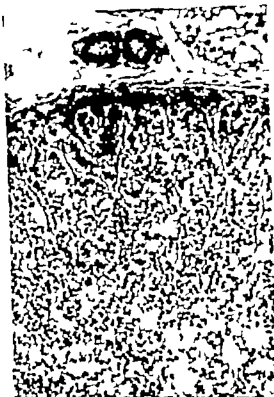


Fig 10 Adrenal cortex from patient 1 showing marked hyperplasia of the zona glomerulosa, which is composed of highly vacuolated cells. Note also two slightly thick-walled arteries at top. Hematoxylin-eosin. 185

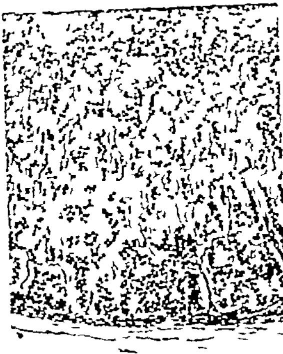


Fig 11 Adrenal cortex from patient 4. The cells of the hyperplastic zona glomerulosa are not vacuolated (compare with Fig. 10). The zona fasciculata is also prominent, but the zona reticulata is very poorly developed. Hematoxylin-eosin. 185

specific ones found in most chronically diseased kidneys. In the distal and collecting tubules many cells stained intensely for tetrazolium reductase and acid phosphatase. There was considerable esterase and acid phosphatase activity in the luminal borders of the cells lining the collecting tubules. The juxtaglomerular cells stained intensely for acid phosphatase.

Microdissection. Microdissection of portion of one of the kidneys from case 1 showed dilatation of the proximal tubules, and the walls of these appeared thinned.



Fig 12 Electron micrograph of part of an immature glomerulus from case 1, showing portion of a small podocyte which lacks foot processes. S = urinary space. Uranyl acetate and lead hydroxide. 19,500

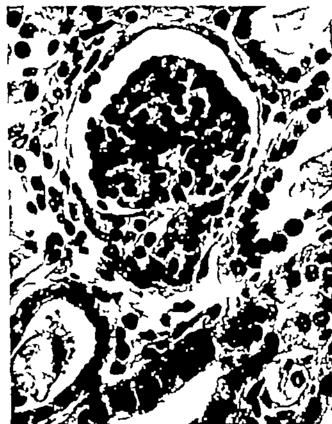


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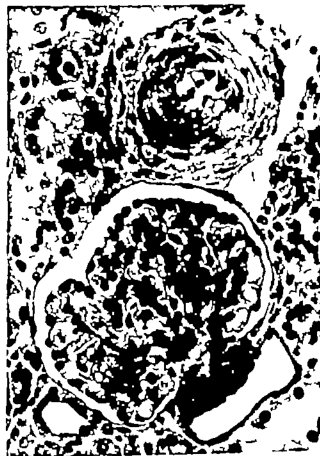


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cretion on a dietary supplement of 68 mEq sodium chloride per day. In the two brothers reported by Visser and associates (43), high sodium intake led to a sharp decrease in plasma renin levels. Finally, two instances of functioning tumors of juxtaglomerular cells (22, 37) have had severe hypertension.

Defect of Sodium Absorption in Proximal Tubule. Dating from the investigations of De Wardener and colleagues (15, 29) an increasing body of evidence suggests that a humoral or third factor independent of both glomerular filtration rate and aldosterone controls the absorption of sodium in the nephron. This humoral or "third" factor is believed to operate in the proximal tubule, where it inhibits sodium reabsorption. A defect in, or deficiency of this factor may be responsible for certain edematous conditions based on positive sodium balance. On the other hand, excess of the factor may be responsible for some states of inappropriate natriuresis and dehydration (8).

Recently a number of investigators (11, 23, 25, 43) have suggested that the basic disorder in Bartter's syndrome may involve a defect of sodium reabsorption in the proximal tubule. By presenting to the macula densa a modified filtrate containing an unusually high sodium concentration, such a defect could lead to hyperplasia and hypertrophy of the JGA together with all the other features of the syndrome—provided the unresponsiveness of the vasculature to angiotensin is explicable on the basis of tachyphylaxis or chronic hypovolemia. In one of the three familial cases studied by Trygstad et al. (42) (1969), urinary potassium wasting and hypokalemia were not corrected by total adrenalectomy and mineralocorticoid replacement therapy. These workers concluded that there was also a defect of potassium absorption in the proximal tubule with the result that abnormally large fractions of both cations are presented to the distal nephron, where aldosterone causes the reabsorption of sodium in exchange for potassium.

It is noteworthy that Cannon and associates (11), on the basis of morphologic findings of arterial sclerosis and glomerulotubular damage and more especially atrophy and degeneration of the cells of the macula densa, have postulated a functional abnormality of the latter in Bartter's syndrome. An alternative explanation of the undoubted changes at the macula densa could be that its cells atrophy or are suppressed as a result of quantitative changes in the amounts of the humoral or "third" factor produced by the tubular epithelial cells proximal to the macula densa. However, there is ample evidence that the macula densa in these patients is also affected by an overall hyperplasia. Furthermore, the work of Thurau et al. (41) suggests that increased sodium concentration at the macula densa of a nephron leads to increased renin liberation by and vasoconstriction affecting that particular nephron. If this be correct, and if there is a defect of sodium reabsorption in the proximal tubule in Bartter's syndrome, the atrophic changes in the macula densa are more likely an expression of exhaustion as a result of chronic hyperstimulation.

The histologic findings in our cases are amenable to interpretation on the basis of the hypothesis just outlined, i.e., that there is a defect of sodium reabsorption and that the macula densa and JG cell changes are secondary. The observations set out in Table IX suggest an overall progression of the process with age. Thus patients 3 and 4, aged 4 and 8 months, showed a significantly higher proportion of immature glomeruli than patients 1 and 2, who were 14 and 11 months old. Our findings also suggest that the proportions of mature glomeruli having obviously hypertrophied JGA, and the size of these JGAs, increase with age. It will be noted (Table IX, col. 4) that the proportion of immature glomeruli having hyperplastic JGAs also seems to increase with age. Rarely, we observed an immature glomerulus whose JGA showed some hypertrophy as well as hyperplasia (Fig. 8). Presumably these were glomeruli that had recently commenced to function.



Fig 13 Another immature podocyte from patient 1 The foot processes are replaced by a continuous cytoplasmic sheet, the epithelial surface of which shows many slender pseudovilli that appear to connect adjacent cytoplasmic areas of the podocyte. S = urinary space. Uranyl acetate and lead hydroxide. × 20 000.

DISCUSSION

Nature of the Basic Defect

Vascular Insensitivity to Angiotensin The basic abnormality in Bartter s syndrome has not been elucidated The hypothesis of defective vascular response to angiotensin advanced by the original authors (2) could theoretically lead to a compensatory increase in the production of renin and angiotensin and secondarily to hyperaldosteronism Were this in fact the mechanism one might expect evidence of sodium retention such as increased extracellular fluid volume with normal or only slightly diminished plasma sodium concentrations This, however has not been the case even when hydration and sodium intake have been adequate Indeed, in many reported cases as in our own urinary sodium wasting has been present in the face of hyponatremia (2 42)

Nevertheless, reduced vascular responsiveness to angiotensin is a well established part of the syndrome Evidence on the response of these patients to infusions of norepinephrine is contradictory Brackett and associates (7) observed a normal pressor response in their patient, but in the patient reported by Imai et al (21) there was a reduced response to norepinephrine infusion It has been suggested that the refractoriness of the vasculature to angiotensin in these patients may be due to tachyphylaxis as a result of prolonged high concentrations of circulating angiotensin (3 7 43) Chronic hypovolaemia may also contribute to the normotensive state of these patients

Autonomous Overproduction of Renin The possibility that Bartter s syndrome may be due to autonomous overproduction of renin does not stand critical analysis Brackett and associates (7) have reasoned that the observed failure of plasma volume expansion by albumin infusions to suppress the excretion (2 19) or secretory rate of aldosterone argues against the hypothesis of vascular insensitivity to angiotensin These workers felt that this, coupled with the observation in their own patient that plasma renin values were elevated on a normal sodium intake and following albumin infusion, pointed to a relative autonomy of the renin-angiotensin system in Bartter's syndrome

In other instances however plasma volume expansion has produced a significant fall in plasma renin concentration (3) or reduction in aldosterone secretion rate Further evidence against autonomy of the renin-angiotensin system in this condition is afforded by the patient reported by Bryan et al (9) in whom sodium deprivation caused a significant increase in aldosterone secretion rate and by the patient of Greenberg et al (19) who showed a marked reduction in aldosterone ex

associates (35) have attributed the arterial hypertrophy without hypertension to angiotensin-induced chronic vasoconstriction in the presence of hypovolemia. While we have no better hypothesis to offer we find it difficult to explain why the arterial changes were always much more severe in the kidneys of our cases and why they were seen outside the kidneys only in our two older patients These observations suggest that the arterial changes may be due to some factor which in Bartter's syndrome and in familial chloride diarrhea is present in high concentration only in the kidneys, which may inactivate most of it. Possibly it is an expression of reflex vasoconstriction initiated by stimuli from the macula densa of each functioning nephron (41) This would also explain the delayed opening up and maturation of glomeruli, especially of the most peripheral nephrons in Bartter's syndrome

Glomerulo-Distotubular Shunts Recently Blava and associates (6) reported that shunts between Bowman's space and the distal convoluted tubule at the macula densa were present in one-third of the glomeruli in renal biopsies obtained from two patients with Bartter's syndrome These shunts were of minute proportions and were identified by electron microscopic examination. It seems reasonable to expect that if such shunts were significantly functional a Fanconi-type syndrome might ensue However not even glycosuria alone has been a feature of Bartter's syndrome Blava and colleagues (6) also described focal thickenings of the mesangial areas and adhesions between the capillary tufts and Bowman's capsule In our cases also, thickenings of the mesangial regions were frequently seen, but the most striking glomerular abnormality was immaturity with poor development of the capillaries and podocytes in association with loss or fusion of the foot processes.

Magnesium Serum magnesium concentrations were consistently and significantly depressed in the two patients of our series in whom this parameter was investigated. The findings may represent a secondary phenomenon, e g., as a result of adrenocortical hyperfunction, or they may reflect renal tubular dysfunction. While the effects of intramuscular magnesium sulphate on the plasma electrolytes of our patients 1 and 2 may in part reflect dehydration, a more fundamental process may also be involved however the nature of this remains to be elucidated.

Genetics Little has been written on the mode of inheritance of Bartter's syndrome, but the condition is generally assumed to be governed by a rare mutant recessive autosomal gene. This is supported by the occurrence of the syndrome in two brothers (43) and even more strongly by the three cases in a sibship of four studied by Trygstad et al. (42) (1969) and by our own series of three siblings and one child of an incestuous union. Modifying genes could explain the extreme severity of the condition in our patients, but other explanations are also possible Chromosomal studies on peripheral blood, marrow and skin from our patients 1 and 2 revealed no abnormality

The syndrome has been reported in Negroes and Caucasians with about equal frequency but, taking relative population sizes into consideration, this may indicate a greater frequency of the mutant gene in the Negro race That all four of our patients were blood group A, Rhesus positive, may be coincidental The presence of pancreatic islet cell hyperplasia in three of our patients may be fortuitous. Growth retardation in these patients is generally believed to be due to chronic potassium deficiency (2, 11 43) Depletion of this cation also renders them more prone to pyelonephritis (33)

The Brain in Bartter's Syndrome The first patient in the classic report of this syndrome ( ) was shown by pneumoencephalography at the age of 5 months to have slight dilatation of the lateral ventricles At 5 years of age electroencephalography repeatedly demonstrated diffuse dysrythmia in the same patient. The second patient in the same report (2) was also shown to have diffuse dysrythmia by

Study of our material also indicated that macula densa changes were related to age and more especially to nephron function. Thus we never encountered an immature glomerulus that had a hyperplastic macula densa In the occasional nephron which displayed evidence of early JG-cell hypertrophy (Fig 8) the macula densa was within normal limits On the other hand the largest maculae densae having most nuclei and lowest epithelium, were always associated with mature glomeruli having large JG-cell masses (Figs 5 6 and 9) and were found exclusively in the juxta medullary regions and deeper cortex.

We interpret these findings to mean that the morphologic abnormality in each nephron develops only when that particular nephron becomes fully functional and that the changes in it progress with the degree and duration of function That there appears to be such a delay in the maturation or initiation of full functional activity of such a high proportion of glomeruli in these patients is probably explicable on the basis of abnormal intrinsic renin angiotensin control of the vasculature of individual nephrons plus quantitative control of renal function by extracellular fluid volume Were the hypothesis of vascular unresponsiveness to angiotensin correct one might expect that all glomeruli would be affected simultaneously and more or less equally Rather does it appear that the basic disorder in each nephron e g., defective sodium reabsorption in the proximal tubule determines the morphologic changes in that nephron, and that these changes will only become apparent after the nephron has functioned significantly for some minimal time This concept may also explain the very small numbers of sclerosed glomeruli seen in our patients who are the youngest yet recorded Presumably progression of the JGA hypertrophy and vascular sclerosis with age would lead to ischemic obliteration of increasing numbers of glomeruli

Cannon and associates (11) found small or miniature glomeruli in biopsies from four cases, and they explained these on the basis of non-specific insults such as anoxia or inflammation in the perinatal period (5) We feel that this explanation is inadequate to account for the age-relationship quantitative and topographic features evident in the autopsy material from the four cases studied by us Our findings strongly suggest that the small glomeruli are immature by virtue of non-function and that they or at least a large proportion of them do eventually become functional—presumably as the age and growth-related demand for increased functioning renal mass overcomes the intrinsic vasoconstrictive mechanism that tends to maintain them in a dormant state Possibly the trace to 1+proteinuria commonly noted in these patients is due to the gradual assumption of function by these immature glomeruli, whose foot processes are non-existent and represented by a continuous sheet of cytoplasm (Figs 12 and 13) Qualitatively similar podocyte changes observed by us in large glomeruli may mean that these particular glomeruli had only recently commenced to function but they could equally mean that the podocytes are permanently altered due to prolonged lack of function or as a result of an inherent abnormality

The renal arterial changes observed in Bartter s syndrome are in keeping with the hypothesis outlined above and explain the high proportion of immature glomeruli and the peripheral location of these Arterial thickening was observed in the periadrenal tissues by Bryan et al. (9) Brackett and associates (7) remarked on it both in the kidney and in a biopsy of gastrocnemius muscle Cannon et al (11) noted this change throughout the kidney but especially in the afferent arterioles. Arterial wall hypertrophy was present in all four of our cases but its degree and extent seemed to increase with age Similar arterial changes have been documented in familial chloride diarrhea a syndrome which resembles that of Bartter in all respects save for the presence of diarrhea and reduced urinary excretion of chloride (34 35) Pasternack and

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electroencephalography when he was 19 years of age The patient reported by Cannon and associates (11) seems to have been mildly retarded mentally

Cerebral changes in Bartter's syndrome are probably nonspecific and related to dehydration and chronic electrolyte depletion Since our patients appear to have had the most severe form of the syndrome yet reported it is perhaps not surprising that three of them showed cerebral changes which were advanced in the two who lived longest and relatively mild in the boy who died at the age of 8 months In our youngest patient, who died at the age of four months, the brain appeared normal

SUMMARY AND CONCLUSIONS

An electrolyte losing syndrome is described in three siblings, including one set of twins, and in an unrelated infant who was the product of incest In most respects the clinical and laboratory findings in these patients were compatible with the condition which has come to be known as Bartter's syndrome In all four of our patients, however symptoms were manifested early in life the disease ran a malignant course and death occurred early Electron microscopic examination of the kidneys from two of our patients showed characteristic structural changes in the glomeruli including immaturity of the podocytes and extensive loss or fusion of their foot processes Light microscopy of the kidneys from all four cases showed an unusually large proportion of immature glomeruli that seemed to diminish slowly with age Some ninety per cent of these small glomeruli were located peripherally The incidence and size of hypertrophied JGA also the degree and extent of hyperplastic arterial thickening appeared to increase with age These findings are discussed in relation to the hypothesis that the basic abnormality in Bartter's syndrome may involve a defect of sodium reabsorption in the proximal tubule, and that this leads to hypertrophy of the JGAs of functioning nephrons with excessive production and release of renin, which causes vasoconstrictive dormancy of the more peripheral glomeruli.

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INFANT FEEDING AND WEANING PRACTICES IN A RURAL PREINDUSTRIAL SETTING

A Sociocultural Approach

DIVA M. SANJUR, Ph.D., M. P. H., JOAQUÍN CRAVIOTO M.D., M. P. H., LYDIA ROSALES, Professor of Fundamental Education; and ANDRÉ VAN VEEN Ph.D.

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INTRODUCTION

In this monograph we report the results of a study concerned with the assessment of the feeding pattern and weaning habits in a group of 125 infants, born in a preindustrial village, in relation to their mothers social characteristics and other presumably related factors. An attempt is also made to understand and explore some of the traditional feeding practices and food ideology prevailing in the village, within the cultural context in which they occur.

Although one would expect common familial eating patterns, nutritional studies in preindustrial villages have found inconsistencies between the infant's diet and the family food intake. Huenemann (1) has reported that in a survey in Peru the greatest proportion of low protein diets in infancy was found in a fishing village where in contrast the adult's consumption of animal protein was the highest of all the area surveyed. Similar discrepancies between adults and children's patterns of food intake have also been reported in Centralamerica by Flores & García (2). Therefore, even if the feeding habits of children depend primarily on the food habits of their parents with modifications in certain respects, it may be misleading to assume the absence of traditional forces shaping the food intake patterns of children, because if they eat differently or are differently fed from the adults there must be a reason.

The pattern of food consumption in any area is generally governed by nutritional, ecological and social factors. The first of these has been widely reported in the literature but it was felt that there was a need for more research of the ecological and social factors affecting infant feeding practices, of the maternal attitudes toward feeding and weaning habits, of the new trends in infant feeding associated with modernization, and several other dimensions yet insufficiently explored in field research except on an anecdotical basis.

The research to be reported is based on a theoretical framework conceptualized as a hypothesis of the biosocial factors affecting Malnutrition" (3 4). Nutritional studies on rural areas of Latin America and West Africa have shown that traditionally the infant tends to be breast fed almost exclusively during a period of no less than six to nine months. As a rule, no significant amounts of other foods are introduced before the child is one-year old, a time at which sudden weaning is frequent. This practice deprives the child of the nutrients of mother's milk, producing a deficiency that cannot be compensated as the child is not permitted a full participation of the foods

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lishing a link that could serve to increase understanding of reasons for nutrition problems, and to help in planning specific nutrition education programs.

THE SETTING OF THE STUDY

Since this report is but one of a series of projects which together form a program designed for the longitudinal ecologic study of growth and development of children in a preindustrial setting, it may be convenient to keep in mind that the general program, in brief, is the follow-up of all the children born in a rural Mexican village of 6000 inhabitants between March 1 1966 and February 28, 1967 These children and their families are being closely observed from the dietary medical, socio-economic and developmental points of view in a coordinated manner with great attention to detail, and so far as possible using validated research instruments. The intention is to follow the children first brought into the study during the prenatal period until they are aged 7 years, the earliest age at which certain crucial psychometric tests can be applied, and at which time the children can all be assessed in the relatively uniform environment of a primary school. The major hypothesis to be tested is that intellectual growth at all stages and performance at school age will be related to nutrition and health status at a much earlier time (8)

In order to examine the complex set of variables with which this investigation is concerned it was necessary to study a large group of children. Estimates of sample needs made it necessary to select a community of sufficient size to provide at least 250 births in the annual cohort to be followed longitudinally The community selected also had to be one containing a considerable range of variation in social conditions and nutritional status, as well as being one in which the population was likely to be cooperative and willing to enroll and to remain in the study Clearly since the study is a longitudinal one, it was essential that the population be relatively stable and that a high proportion of the families and infants enrolled for study at birth be likely to continue to live in the community for the duration of the period of inquiry

The community chosen met these requirements. Selection was based on previous experience with rural communities and field studies. In one of these studies the present village was a participating community and had exhibited a high level of population stability over time, excellent degrees of cooperation, a wide range of variation in social, economic, familial, and health attributes, and was of sufficient size to have an annual birth expectancy of 300.

Demographic aspects

The village is located in a semitropical subhumid zone in south western Mexico in a primarily agricultural region in which arid hillsides alternate with fertile valleys and meadows. It is at an altitude of between 900 and 950 meters above sea level, and has a hot subtropical climate modified by its altitude. The median annual temperature is between 23 and 25 degrees centigrade in the shade, and ranges from chilly winters to very hot summers in which daily high temperatures of 40 C are not uncommon. A small river whose waters are used both for irrigation and for laundering and other general purposes runs through the village

As is characteristic of Mexican rural villages in this region the arrangement of the town devolves from a central shaded plaza and from this center proceeds centripetally along a series of unpaved and rutted dirt streets which are related to one another to form roughly quadrangular blocks.

The area surrounding the townsite is entirely agricultural with sugar cane constituting the major commercial crop A small amount of cotton and rice are also grown commercially Interspersed among the large commercially organized fields are small family parcels and rentable areas that are used by the villagers for the production of food crops, principally corn,

available to the older members of the family It has been noted that in these rural communi ties there are lists of foods that are prohibited to infants and children. Sometimes this is a valid concept only during sickness periods, but in many cases the prohibition is extended to other life periods even when the child is in a healthy state. It is our suggestion that these practices constitute the natural history of food habits in traditional rural areas, and our re search attempts to evaluate some of these propositions in our interest in further identifica tion of the nature and transcendence of nutritional problems in infancy and childhood.

Since there is a great number of reports dealing with the nutritional composition and content of the food ingested by infants and children living in areas where malnutrition is prevalent it was decided that, instead of using the classical nutritional approach it could be profitable to turn to methods and techniques of social science It was hoped that in evaluat ing the infant s food intake during his first six months of life some sort of food scale could be found that would indicate an underlying level of complexity in the diet consumed, as shown by increasing scale steps Moreover it was thought that either the levels of the infant or the family food scales might correspond to cer tain sociological indices in such a way that complexity in the dietary pattern could be cor related with a similar complexity in other aspects of the family's living.

As thought, perception and practice be come more complex in one sphere of life, there would be expected to occur an increased com plexity in thought and practice in other spheres Thus it follows that with more education and/or income or some other similar increase in life complexity one would anticipate the infant and/or family dietary pattern to also become correspondingly more complex. Con sequently one would expect more modern food concepts and practices to be found in the thinking and belief orientation of such groups within the population.

Accordingly this study looks closely at the infant s diet as it relates to the family s food intake, and to the reasons for discrepancies. As a corresponding family food scale was also developed, it was possible to explore probable associations of both scales with the variables hereby conceptualized as indicators of the fam ily "way of life" as evidenced by a multi faceted index of

Parent s socioeconomic status
Family s reference factors (age, size)
Family s health variables
Length of lactating period
Mother s educational level
Mother s social orientation
Mother's social participation
Mother's exposure to mass media

Defining differentiation as the capacity of a social system to process a diversity of infor mation types, Young (5 6) has postulated that families can be classified as differentiated and undifferentiated in terms of the number of functions performed, the heterogeneous role content, and the diversity of available cognitions. Since this concept is explored by a variety of social indicators included in the present study such as mass media exposure, visiting pattern, and a variety of foods consumed as shown by scalograms, it was thought that the research offered a good opportunity to test Young s concept of differentiation

Finally the analysis of the data lead us to test Reeder s concept of specificity" of elements of decision making and social action (7)

One of the problems and pitfalls of a field nutritionist who is attempting to determine the relative importance of multiple factors affect ing infant nutrition—either as independent, intervening or dependent variables—is the high degree of correlation that exists among some of these dimensions. What may be thought of as a cultural or even racial influence may well be an income factor or vice versa

The attempt to explore these relationships through a sociocultural approach is an uncon ventional avenue in nutrition research. The idea has been developed in a search for estab-

lishing a link that could serve to increase understanding of reasons for nutrition problems, and to help in planning specific nutrition education programs.

THE SETTING OF THE STUDY

Since this report is but one of a series of projects which together form a program designed for the longitudinal ecologic study of growth and development of children in a preindustrial setting, it may be convenient to keep in mind that the general program, in brief, is the follow-up of all the children born in a rural Mexican village of 6000 inhabitants between March 1 1966 and February 28, 1967 These children and their families are being closely observed from the dietary medical, socio-economic and developmental points of view in a coordinated manner with great attention to detail, and so far as possible using validated research instruments. The intention is to follow the children first brought into the study during the prenatal period until they are aged 7 years, the earliest age at which certain crucial psychometric tests can be applied, and at which time the children can all be assessed in the relatively uniform environment of a primary school. The major hypothesis to be tested is that intellectual growth at all stages and performance at school age will be related to nutrition and health status at a much earlier time (8)

In order to examine the complex set of variables with which this investigation is concerned it was necessary to study a large group of children Estimates of sample needs made it necessary to select a community of sufficient size to provide at least 250 births in the annual cohort to be followed longitudinally The community selected also had to be one containing a considerable range of variation in social conditions and nutritional status, as well as being one in which the population was likely to be cooperative and willing to enroll and to *remain* in the study Clearly since the study is a longitudinal one, it was essential that the population be relatively stable and that a high proportion of the families and infants enrolled for study at birth be likely to continue to live in the community for the duration of the period of inquiry

The community chosen met these requirements. Selection was based on previous experience with rural communities and field studies. In one of these studies the present village was a participating community and had exhibited a high level of population stability over time, excellent degrees of cooperation, a wide range of variation in social, economic, familial, and health attributes, and was of sufficient size to have an annual birth expectancy of 300.

Demographic aspects

The village is located in a semitropical subhumid zone in south western Mexico in a primarily agricultural region in which arid hillsides alternate with fertile valleys and meadows. It is at an altitude of between 900 and 950 meters above sea level, and has a hot subtropical climate modified by its altitude. The median annual temperature is between 23 and 25 degrees centigrade in the shade, and ranges from chilly winters to very hot summers in which daily high temperatures of 40 C are not uncommon. A small river whose waters are used both for irrigation and for laundering and other general purposes runs through the village.

As is characteristic of Mexican rural villages in this region the arrangement of the town devolves from a central shaded plaza and from this center proceeds centripetally along a series of unpaved and rutted dirt streets which are related to one another to form roughly quadrangular blocks.

The area surrounding the townsite is entirely agricultural with sugar cane constituting the major commercial crop. A small amount of cotton and rice are also grown commercially Interspersed among the large commercially organized fields are small family parcels and rentable areas that are used by the villagers for the production of food crops, principally corn,

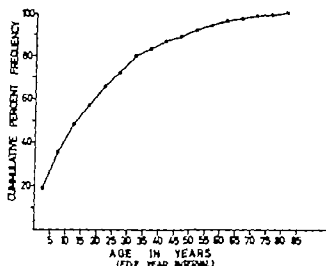


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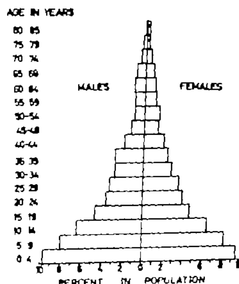


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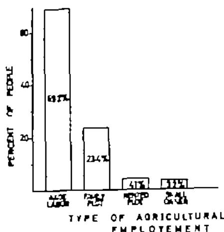


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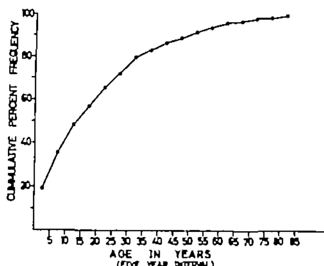


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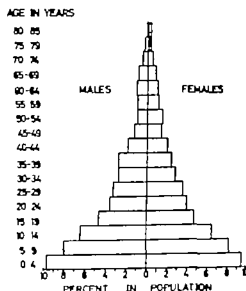


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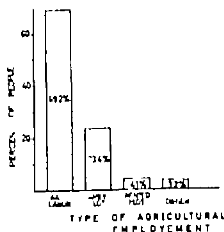


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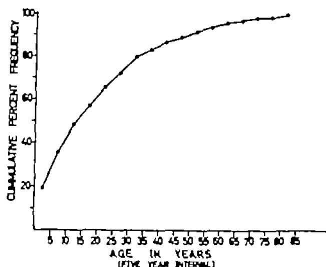


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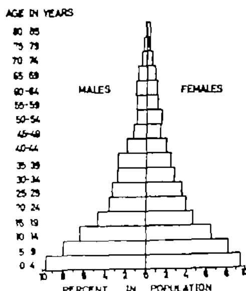


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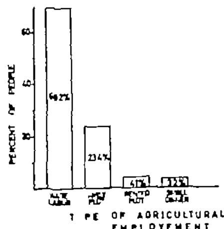


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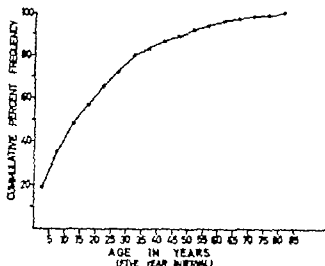


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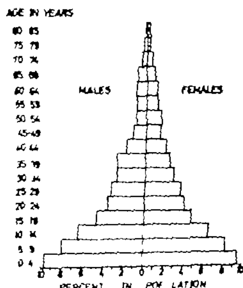


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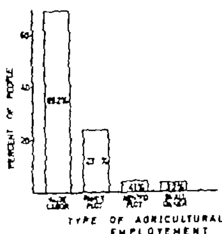


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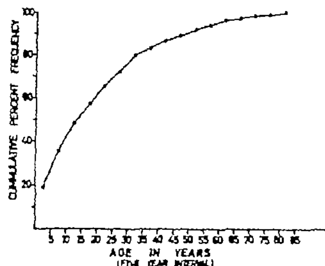


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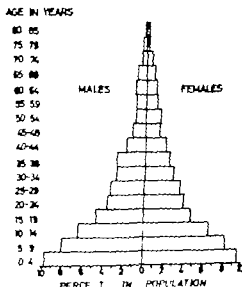


Fig 2 Age pyramid by sex.

ing home-made tea. Carbonated beverages are also popular especially those with fruit flavor which often are taken at lunch. *Manzanita* a carbonated beverage with apple flavor is very much preferred by the mothers when they are sick.

Lard and cottonseed oil are the main types of cooking fat used. *Nata* or *crema* (milk cream) is sometimes consumed, but butter seems not to be consumed at all by the families. The only time they reported buying and using it was once a year in November when traditional customs dictate preparation of elaborate dishes and special cakes, which are taken to the cemetery as offering to their dead relatives. This is a symbolic offering only since the prepared dishes are later brought back home and consumed by the family

Food preparation and preservation

Although food preparation is rather simple and routine, it may very well take a great part of the mother's time in relation to her other tasks such as care of the children, laundry housekeeping, etc. If she has an older daughter she usually gets help in the shopping, cooking and distribution of meals, but the final decision as to what foods to buy or eat, day by day are left to the mother If there is a case of a young wife living with her in-laws, there decisions will rest with the mother in-law Generally foods are boiled or fried. There are a few instances of foods roasted or charcoal-broiled. Baking is rarely done because few families own ovens.

Drying is the most common method of food preservation known and used in this village. Beef, pork or fish are the foods most commonly dried, by way of hanging them up in the kitchen.

The kitchen itself may be simply an area of a one-room home or a separate room apart from the living quarters. Eating seems to be done in the kitchen. The food is eaten from metal or glass plates. Mugs are used for drinking. Tortillas often serve in place of forks or spoons and this way of eating is called *sopear* by the villagers.

Among the most commonly used kitchen equipment and utensils are the following: *Tortilleras* (tortilla press) where tortillas are shaped and then baked directly on a *comal* (a piece of hot metal) over the fire. A *molcajete* (clay or stone mortar) is used for grinding chillies, ptomates and other condiments with a *tejolote* (stone pestle) to prepare the sauce described previously Utensils may differ in quantity among families but usually not in kind. *Ollas* (deep pots) of pottery or metal are used for holding and cooking liquids. Many housewives pride themselves in having a large well-chosen collection of the pottery ones, as these come in different shapes and sizes. A *sartén* (metal skillet) is used for frying. Cooking is done primarily over a wood fire in a *tlecuitl* (an open clay fireplace) Some families may posses bottled gas stoves, but they still prefer the *tlecuitl* for baking the tortillas.

ANTECEDENTS AND BACKGROUND

In reviewing the literature on infant feeding practices in several parts of the world, whether it is India, Mexico or Thailand, one encounters an astonishing number of rather similar basic cultural forms, particularly within the context of peasant societies, with some variations, of course, accounting for particular features.

Man chooses food not nutrients and much of his dietary pattern is thus built from experiences over centuries and not necessarily from the newer scientific knowledge on nutrition. Dietary patterns, as part of total socio-cultural systems are major components of belief and behavior in traditional rural societies. Nutrition experts envisage the nutrition of the mother and the child as a continuum, so much so that some believe in the old Chinese saying that infant feeding begins in utero, and regard the child as being one year old at birth.

This review of literature will attempt to highlight several crucial periods in infant feeding:

sauce Cut slices of hard boiled eggs usually accompany the *sopa seca* when this is made of rice *Jitomate* (tomato) *Tomate* (green tree tomato) and *chili* (hot pepper) are bought and consumed in great amounts as components of the *salsa* (hot sauce) almost an imperative accompaniment in the meals, as the tortilla and beans are This *salsa* may be used as spread in the tortillas, or just merely to prepare other dishes

The most commonly eaten animal protein foods are eggs, pork, beef and chicken Meat is usually prepared in *mole* or *guiso* (stew) Local cheese is also consumed and is usually prepared in *quesadillas* (folded tortillas with melted cheese or squash blossoms, etc)

Milk, when consumed is usually sweetened with sugar and taken hot with a flavoring of coffee chocolate, or cinnamon or it may be taken as *atole* (gruel) *Atoles* are usually consumed especially by children or lactating women, in the evening meal

There is an abundance of various tropical fruits in the market place and the families that can afford to buy them choose from among such seasonally available items as bananas, oranges, papaya, mango pineapple, apples, and quite a number of Mexican ones such as *tunas capulines nananchils mamey* and many others. Among the fruits plátano (banana) seems to be the most popular one Limes are also consumed by the majority of the families, not only in home-made refreshments but also added to the soups, salads, etc There is at least one lime tree in almost every patio behind the house Children also seem to like limes, which are consumed several times a day between meals.

There is a wide supply of vegetables in the market place among which are carrots, tomatoes pumpkin squash green peas lettuce, cabbage, and quite a number of Mexican green leaves such as *pápalos pipizca verdolaga quelite* and others. Their consumption seems to be conditioned by income rather than availability or acceptance.

Interestingly enough, some women had their own classification of vegetables. *verduras de campo* are those green leaves growing wild in the open field, where they just take them when they happen to be near the fields, and *verduras de pueblo* were those vegetables that have to be bought in the plaza market.

Three main meals are eaten during the day *desayuno* and *almuerzo comida* and *cena*—taking place in the morning, early afternoon and evening respectively The main meal of the day is the comida (1 00 to 3 00 p.m.) and has the most variety of them all. If meat, eggs, longaniza (sausages) chicharrón (fried pork skin) or any other protein food item is eaten during the day it is most likely to be eaten at this meal. There is an interesting breakdown, though, in the morning meal for some of the families This may be especially true in those households where the mother has to get up very early to prepare lunches for her early riser husband. If this is the case, they may have a *desayuno* (5 30 to 7 00 a.m.) consisting of bread, coffee or tea Then an hour or a couple of hours later the almuerzo (8 00 to 9 30 a.m.) consisting of tortilla, beans, coffee or tea, and in some families even eggs, meat, bread, hot milk or avocado may also be consumed The evening meal (6 00 to 8 00 p.m.) may be just bread or sweet rolls, tea or coffee plus tortillas and beans, some families reported the *cena* as lo que sobra de la comida" (left overs from noon), or "lo mismo" meaning the same as they had during noon time Usually tortillas are prepared at noon and in sufficient amounts as to make sure they will have enough of them to be consumed again in the evening together with the beans.

Water is the usual beverage and is nearly always obtained from numerous local hydrants or home pipes. Bottled water may also be available to those that can afford it. Black coffee is about the most common breakfast beverage and tea, the evening beverage.

Té de hojitas as referred by the mothers is the local tea made by steeping fresh leaves—from a citrus tree or spearmint plant—in hot water Cinnamon bark is also used for prepar

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Dietary deficiencies of the pregnant and lactating women are by no means restricted to poor rural areas in developing countries.

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B. Breast Feeding and Weaning

One of the most significant features encountered in reviewing the literature—with regard to the nutrition of infants belonging to the poor socio-economic groups—is the fact that lactation performance of their mothers is evidently not unsatisfactory, at least for the first few months after delivery. Instances of inability to breastfeed the infant, which are frequently reported among the sophisticated high socio-economic group, are extremely rare among the poor mothers. Moreover, extensive field surveys carried out in poor Indian villages have indicated that there is almost an inverse rela-

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In a recent "Canadian Nutrition" publication, Anderson (18) reports a study of food habits in 135 expectant mothers during the latter part of their pregnancy. The author notes that these women were probably a privileged group with a good income and high educational standard, since all were referred to the prenatal classes by their private physicians. A lack of knowledge about nutritious foods, or failure to apply that knowledge to themselves, was revealed in the survey. Only 9.6% included the recommended amount of milk specified for expectant mothers in Canada's Food Guide. In addition, one third of them did not include the required daily amount of fruit, while the consumption of other foods such as cereals, sugar, jams, candy, cookies and soft drinks was quite pronounced.

B. Breast Feeding and Weaning

One of the most significant features encountered in reviewing the literature—with regard to the nutrition of infants belonging to the poor socio-economic groups—is the fact that lactation performance of their mothers is evidently *not unsatisfactory* at least for the first few months after delivery. Instances *of inability to* breastfeed the infant, which are frequently reported among the sophisticated high socio-economic group, are extremely rare among the poor mothers. Moreover, extensive field surveys carried out in poor Indian villages have indicated *that there* is almost an inverse rela-

A. Maternal nutrition (diets in pregnancy puerperium and lactation)
B Breast feeding practices and weaning time, and
C. Supplementary feeding practices.

These periods—so arranged for organization purposes and by no means mutually exclusive categories—will be discussed using cross-cultural examples mainly from developing regions of the world.

A Maternal Nutrition

Kevany (9) in a review of the nutrition problems of the pre-school child in Latin America points out poor maternal nutrition as one of the specific ecological factors contributing to these problems He notes that in the majority of the under nourished women in Latin America, food intake of the woman is not improved during pregnancy Poverty ignorance, or mere apathy may be some of the influencing factors. At the same time the pregnant woman continues to do heavy physical work that demands more energy output. Consequently she gains little or no weight during this period In view of the physiological priorities of the fetus, Kevany concludes that maternal undernutrition is unavoidable

The diet of the mother during lactation is very much characterized by an increase intake of those food items or substances associated with milk output. Gopalan and Belavady (10) report that among poor Indian communities several articles of diet are believed to be galactogogues In the villages studied garlic, cotton seed and tamarind were claimed to be galactogogues These substances are actually administered to the mother to promote lactation. In some cases their consumption is continued for some time thereafter with a view to maintain lactation

The diets of pregnant women are influenced by the same factors that are important in determining diets in general. A great deal is attached to economic factors Alteration of diet during pregnancy may occur in more industrial societies due to the effect of obstetric advice aimed at limiting the amount of weight gain or pregnant women may themselves alter their diets as a result of cravings for a particular kind of food. Cultural factors may also play a role Desires for particular foods or food preparations are called *antojos* in Latin America, where there is the widespread belief that unfulfilled desires of pregnant women may result in birthmarks"

Jellife (11) who has done extensive research in several parts of the world with a particular cultural approach to these practices, reports special dietary attitudes during the puerperium. He classifies these practices as either

(*a*) nutritionally beneficial as with the *caldo* (broth) made with beef or chicken employed in Guatemala, or

(*b*) harmful customs as in the case of the Chinese mothers in Singapore where food is restricted for forty days after delivery

Cultural meal patterns also have strong implications for maternal and infant nutrition. Cuthbertson (12) reports that in most African households the person having first choice of food is the husband or father He is followed by the other productive members of the family i.e., elder sons and younger brothers. Other older children come next and often the mothers and toddlers are last to be considered

Nurge (13) in a study of infant feeding in a Filipino village found that before delivery a pregnant woman does not eat special foods to nourish her baby or strengthen herself During the lactation period, however these mothers were concerned with their overall general health. Among the traditional procedures which are believed to ensure an abundant flow of milk are liquids of various kinds, especially broth from vegetables meat or fish. Clams and crabs were favorite sea foods because of their supposed milk making properties Milk of any kind was not popular although some of the more educated women drank diluted evaporated milk. As to food avoidances for lactating mothers, Nurge reports the most common item

which is deemed harmful was anything sour—such as oranges and lemons.

Mill's study (14) on the influence of economic level in the feeding of *Chinese infants* in the first year also reports on the traditional food customs observed by lactating women. On this particular study it was noticed that the financial and educational advantages of the wealthier women resulted in a modification of their traditional food customs.

Kelly (15) contends that while few food restrictions are imposed on the Mexican pregnant women, they are legion after birth. Sometimes the choice is so rigidly limited by tradition that the woman cannot approximate a balanced diet. Often foods are classified as "hot or cold" irrespective of actual temperature. In general, most fruits and vegetables are considered cold and were not consumed by the women. She reports that some of the women studied subsisted on hot" foods until the day they leave their bed, and specifically these were limited to chocolate, coffee, cinnamon, tea, certain kind of gruel and toasted tortilla. The meat of a laying hen (and not of any other fowl) was considered acceptable. Kelly notes that women excluded all fruit and vegetable for 30 to 40 days and some women refused these foods for the whole period of lactation, as they believed that their consumption would cause diarrhea in the infant.

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or by actual geographical separation, as by sending the child away to a relative.

The weaning process has been associated with diarrheal disease in the technically under developed countries. Gordon, et al. (23) report that in the Guatemalan highlands the initiation of the weaning process with the addition of other foods besides breast milk is associated with a greatly increased frequency of diarrheal disease, whether weaning begins at an early age or relatively late.

An indirect index of the population's nutritional condition is the infant mortality rate, which is notoriously high in Chile, though it is considerably lower in the preschool children. Moenckeberg (24) postulates that one of the reasons might be the short breast-feeding period frequently observed in Chilean mothers. In a group of 325 mothers studied, it was observed that at the third month only 30 per cent had enough milk for breast feeding, thus meaning that hypoalimentation and intestinal infections my set in at a very early age in Chilean children.

Kevany (9) draws the attention to another dimension in comparing weaning time versus child mortality rates. In those countries where early weaning occurs, mortality from nutritional disease has its peak in the first twelve months of the child's life, while in those countries where late weaning is practiced, such peak tends to be delayed" and occur in the second or third year

There are not many studies about weaning time in the Latin American countries but variations do occur In Chile, as mentioned above, weaning takes place during the first months of life In Guatemala, on the contrary weaning takes place at the end of the second year or even later while in Colombia, an intermediate situation is found where lactation may last from six to nine months. Kevany describes multiple factors accounting for the direct association between mortality rates from nutritional diseases and weaning time. Abrupt weaning, low social priority of this group within the family a highly contaminated environment, illiteracy and a sudden transfer of the child to a modified, deficient adult diet seem to be the relevant ones.

C Supplementary Feeding

This is another crucial period in an infant's life and nutrition experts considered it the most difficult problem in practical nutrition in preindustrial countries After the sixth month, breast milk becomes progressively inadequate and supplementary feedings providing for adequate amounts of protein are called for

In poor Indian communities supplementary feeding of infants is started by the six month, but the supplements are mostly modified versions of the poor adult diet (11).

Social factors, such as place of residence or race, may play a role in shaping infant feeding patterns. A recent comparative study of feeding habits in Thailand was undertaken in 90 village families and 114 town families (25) A striking difference in the age of introduction of breast supplements was noted. About 60 per cent of village families started their infants on rice feedings on the third day In contrast, only 2.7 per cent of the town families stated they fed infants rice during the first weeks of life City children were fed vegetables and meat somewhat earlier than village children. Few village children ate family food until they were over 36 months old, while approximately 40 per cent of city families allowed children to eat with the family during the second year of life.

In a review article of the nutritional problems of children in Central America and Panama, Scrimshaw and co-workers (26) highlight the great variations in feeding practices within the Central American Isthmus. They point out the varied racial origins, Indian, white and negro, as one of the strong variables that may account for this variation.

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tionship between the position of the mother in the socio-economic scale and her lactation. Gopalan and Belavady's studies (10) of aspects of lactation in Indian women belonging to the poor socioeconomic group found that infants were invariably fed at breast for prolonged periods. Breast feeding was usually started within two or three days after delivery and was continued into the second and third year of life In contrast, Mill's study of Chinese mothers showed the trend for wealthier women to wean earlier

In a survey covering different parts of South India prolonged breast feeding seemed to be the practice Rao and colleagues (19) found that among poor communities 92% of infants were at the breast at the age of six months, and over 50% at the age of eighteen months. One child in every five was at the breast beyond two years of age, one in eight was still breast fed even at the age of $2^1/_2$ years, and 2% were not fully weaned at the age of three years

In another study of the hill tribes of South India, Bhavani, Balavady and co-workers (20) found similar results of prolonged breast feeding. In a large majority of the tribal children complete weaning took place around the third year Weaning was mostly determined by the onset of the next pregnancy and not by any definite ideas or traditional beliefs regarding the optimum time for weaning. Breast feeding was done on demand and not according to schedule The frequency of feeding depended upon whether the mother was staying at home or working.

In a study conducted by Gans (21) at a number of West Indian out patient clinics in London England he notes that the breast feeding performance of the great majority of West Indian mothers is markedly superior to that of their noncolored sisters In spite of their excellent lactation potential, discontinuation of breast-feeding was almost universal once maternity benefits ceased, because the great majority of mothers had to return to work. The reason for discontinuing breast feeding among these West Indian mothers was therefore an economic one and not, as Hussain (17) found among Pakistanis mainly due to imitation of British infant feeding practices

Whether or not a woman believes she can become pregnant again while lactating sometimes has a bearing, one way or another on the length of time she will breast feed the child. In this respect, Nurge (13) notes that the Filipino mothers she studied were almost divided in their opinion as to the effect of lactation on possible impregnation Almost half the women stated unequivocally that they could not get pregnant while breast feeding, and a little over half believed, or knew through experience that they could conceive while lactating. The idea that prolonged breast feeding is a contraceptive function is suggested by Jellife (11) as being widely held in many parts of the world. He acknowledges that this may be partially true, and quotes a study done by Gioisa in 1955 on the incidence of pregnancy in lactation in 500 cases, which seemed to indicate that lactating women are less likely to conceive

A recent study reported prolonged breast feeding practices in a large number of children living in rural surroundings in Central Java (22) In several villages more than one half of the children between two and three years old were receiving breast milk, and nursing continued for an appreciable number of three years old.

Jellife (11) contends that the reasons for stopping breast-feeding in tropical peoples are various, but traditionally this is most commonly dictated by the onset of another pregnancy as it is widely held that if this is not done the breast milk will become harmful, poisonous, or in some way detrimental to the suckling child. He also observes that the process of separating the child from the breast is sometimes reinforced by the application of bitter or unpleasant substances to the breast (tobacco garlic, red pepper etc.) by offering the child certain food delicacies as a sort of compensation, by sleeping apart from the mother

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or sugar water diet, grossly deficient in all nutrients The situation is even worse by the giving of purgatives on the supposition that diarrhea is being caused by "worms"

In Costa Rica they found great variations in the breast feeding months when compared to the average for Central America In the situation revealed in the rural zone of Turnalba, 38 per cent of the women were no longer nursing their babies at six months and by the end of one year only 26 per cent of the babies were still breast fed Of those infants who were still receiving milk from the mother it is probable that the quantity received was grossly inadequate Supplementary food is usually not given until the child is nearly a year old, and then he is offered certain of the adult foods such as *tortillas* and beans and *atoles* (gruel) of relatively low nutritive value At one year of age only 64 per cent of the children received fruit or fruit juice 46 per cent whole milk 36 per cent cereal 21 per cent egg, and 9 per cent meat

In short Scrimshaw and co-workers conclude that the most striking finding about the diets of children, and especially young children was the lack of protective" foods The percentage of children using green and yellow vegetables was remarkably low and a great many living in rural areas consume no milk at all. Eggs were consumed only infrequently and the amounts of meat or fish which were given are extremely small

Jelliffe (27) reports an interesting field study of health and nutrition done on the children of the San Blas Indians of Panama. A total of 129 infants and 377 one to-four years old were studied He reports that breast feeding was successfully carried on by almost all mothers. Other food was introduced to two thirds of the children in the second six months of life This was most usually mashed ripe banana, yams, cassava or malanga, all boiled and made into a puree Earlier introduction of foods was more usual among the sophisticated mothers. In the more traditional group breast feeding usually appeared to be uneventful, permissive and prolonged until and through the subsequent pregnancy

Communal" breast feeding was the rule, whereby a child was suckled by a relative if the mother was not available. Fish, the main available source of protein apart from breast milk was rarely used in the first year of life by mothers who mostly regarded breast milk as sufficient by itself Fish was thought as dangerous to infants because of the bones. Fruit although growing in considerable variety was eaten in season but not given to the young child Basically the young San Blas Indian child received small but slowly increasing amounts of the adult diet in the second year of life

Flores and García (2) compared the specifically determined foods given to 32 Guatemalan children from weaning to five years of age with the diets of their whole families. In the one to two years age group they found that less than one-third of the children received milk Tortillas and a thin black bean soup were the first foods introduced into the diet these two foods plus wheat bread were fed to almost all the children in the 1 to 2 years group Other foods frequently found in the diets of this group were rice and noodle soups, tomatoes, black beans and small amounts of potatoes.

Flores and co-workers (28) in another study found that of the 300 Guatemalan Indian children included in their sample all under twelve months of age were breast fed. Foods were gradually introduced into the diet. The greatest restriction of food was observed to occur in the diets of the 1 to 2 years age group. Children in this group received cow s milk when it was available, and small amounts of white bread, coffee, tortillas, black beansbroth and oatmeal.

In 1961 Orozco and Ramos-Galvan (29) studied the feeding of 305 malnourished infants under 2 years of age in the city of Uruapan Michoacan, Mexico They found that 64% had received breast feeding during the first year of life, 38% continued with breast milk for 13 to 18 months and 16 per cent for

19 to 24 months. There are various opinions (the authors contend not based on statistical data) on the prolonged use of breast feeding which is frequent among Mexican women, and on the reasons for such conduct. Considering that in their sample one-sixth of the children were breast-fed for 2 years, the authors have the opinion that it is difficult to assume that such a prolonged use of maternal milk could further the purpose of maintaining a good state of nutrition in malnourished children.

Research studies by Chavez et al (30 31) in 21 rural communities of Mexico have shown that the daily diet of the preschool child was relatively lower than that of the adult. The noticeable deficiency of fats is responsible for a low source of energy. Besides calories there is also a low intake of proteins, calcium, vitamin A, ascorbic acid and riboflavin. Ramos-Galván (29) also points out that similar deficiencies in diets were found when research was carried out several decades ago and he adds that it seems conclusive that neither the feeding habits nor the average amounts ingested have undergone any substantial change.

In this respect, it seems interesting to discuss briefly two studies of the dietary patterns of young children done in the same Mexican community but at two different points in time, which indeed exhibit changes in the dietary patterns, or at least in its trends.

A report by Pérez Navarrete et al. (32) of feeding patterns during the first year of life in "The Land of the White Dust" Mexico, gave the following results: breast-feeding was the only method of feeding used for 91 per cent of the children during the first six months. A combination of maternal and cow's milk formula alone served 7 per cent in the birth through five month age group and a formula based on cow's milk was the sole source of nutrients of the remaining 2 per cent of infants. Foods in addition to milk were not observed in the diets of any infants less than six months of age. Within this pattern, these children became gradually malnourished.

A study done six years later in the same village by Morrow (33) disclosed a lower percent age of children in both age groups feeding exclusively on breast milk, and a correspondingly higher per cent of infants in both age groups who had other foods included in their diets. In general, even though there are differences between the two studies, both found similar patterns of diminishing concentration on milk in the diet with increasing age.

Other General Factors Influencing Feeding Practices

Contradictory reports are found in the literature as to how Latin American villagers value health. Positive values and attitudes are reported by Burgess, Adams and Freedman, while Sollen and Scrimshaw and Foster report on some negative practices observed.

Burgess (34) contends that in Central America and South America, food is valued as conducive to good health and strength, being there a real desire to eat well if funds permit, and to spend any extra money on food rather than on clothes or jewelry as happens in parts of Indonesia, or on cattle or land as is done in some parts of Africa. Adams (35) also reports that some traditional systems of medicine contain a definite recognition of personal responsibility in the avoidance of illhealth. Furthermore, Burgess notes that, in at least some parts of Central America, there seems to be a useful empiricism in the mother's attitude as to what her child can and cannot eat. Each child in the family is treated individually in this respect, and food is not withheld from one child because it appeared to disagree with another. Freedman also reports (36) that pregnant women are encouraged to eat well and to drink strengthening gruels and *caldos* (beef or chicken broths) during lactation.

On the other hand, Foster (37) is of the opinion that although Latin american villagers know that food is related to health and illness, they tend to see this relationship in a negative rather than positive fashion. He adds that there is little idea that a balanced diet promotes good health, rather a person who enjoys good

or sugar water diet, grossly deficient in all nu trients The situation is even worse by the giv ing of purgatives on the supposition that diarrhea is being caused by "worms"

In Costa Rica they found great variations in the breast feeding months when compared to the average for Central America. In the situation revealed in the rural zone of Turrialba, 38 per cent of the women were no longer nursing their babies at six months and by the end of one year only 26 per cent of the babies were still breast fed Of those infants who were still receiving milk from the mother it is probable that the quantity received was grossly inadequate Supplementary food is usually not given until the child is nearly a year old and then he is offered certain of the adult foods such as *tortillas* and beans and *atoles* (gruel) of rela tively low nutritive value. At one year of age only 64 per cent of the children received fruit or fruit juice 46 per cent whole milk 36 per cent cereal 21 per cent egg, and 9 per cent meat

In short, Scrimshaw and co-workers con clude that the most striking finding about the diets of children, and especially young chil dren was the lack of protective" foods. The percentage of children using green and yellow vegetables was remarkably low and a great many living in rural areas consume no milk at all Eggs were consumed only infrequently and the amounts of meat or fish which were given are extremely small

Jelliffe (27) reports an interesting field study of health and nutrition done on the children of the San Blas Indians of Panama. A total of 129 infants and 377 one to-four years old were studied He reports that breast feeding was successfully carried on by almost all mothers. Other food was introduced to two thirds of the children in the second six months of life This was most usually mashed ripe banana, yams, cassava or malanga, all boiled and made into a puree Earlier introduction of foods was more usual among the sophisticated mothers. In the more traditional group breast feeding usually appeared to be uneventful, permissive and prolonged until and through the subse quent pregnancy

Communal" breast feeding was the rule, whereby a child was suckled by a relative if the mother was not available Fish the main available source of protein apart from breast milk was rarely used in the first year of life by mothers who mostly regarded breast milk as sufficient by itself Fish was thought as dangerous to infants because of the bones. Fruit although growing in considerable variety was eaten in season, but not given to the young child Basically the young San Blas Indian child received small but slowly increasing amounts of the adult diet in the second year of life

Flores and García (2) compared the spe cifically determined foods given to 32 Guate malan children from weaning to five years of age with the diets of their whole families. In the one to two years age group they found that less than one third of the children received milk Tortillas and a thin black bean soup were the first foods introduced into the diet, these two foods plus wheat bread were fed to almost all the children in the 1 to 2 years group Other foods frequently found in the diets of this group were rice and noodle soups, tomatoes, black beans and small amounts of potatoes.

Flores and co-workers (28) in another study found that of the 300 Guatemalan Indian children included in their sample all under twelve months of age were breast fed. Foods were gradually introduced into the diet. The greatest restriction of food was observed to occur in the diets of the 1 to 2 years age group. Children in this group received cow s milk when it was available, and small amounts of white bread coffee, tortillas, black beansbroth, and oatmeal

In 1961 Orozco and Ramos-Galvan (29) studied the feeding of 305 malnourished infants under 2 years of age in the city of Uru apan, Michoacan, Mexico They found that 64% had received breast feeding during the first year of life 38% continued with breast milk for 13 to 18 months and 16 per cent for

19 to 24 months. There are various opinions (the authors contend not based on statistical data) on the prolonged use of breast-feeding which is frequent among Mexican women, and on the reasons for such conduct. Considering that in their sample one-sixth of the children were breast-fed for 2 years, the authors have the opinion that it is difficult to assume that such a prolonged use of maternal milk could further the purpose of maintaining a good state of nutrition in malnourished children.

Research studies by Chavez et al (30 31) in 21 rural communities of Mexico have shown that the daily diet of the preschool child was relatively lower than that of the adult. The noticeable deficiency of fats is responsible for a low source of energy. Besides calories there is also a low intake of proteins, calcium, vitamin A, ascorbic acid and riboflavin. Ramos-Galván (29) also points out that similar deficiencies in diets were found when research was carried out several decades ago and he adds that it seems conclusive that neither the feeding habits nor the average amounts ingested have undergone any substantial change.

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a direct relationship was found between the level of growth retardation as measured by body weight and the schooling of the father. In a subsequent study years later (41) in a village of the Guatemalan Highlands the only strong positive association found between background circumstances and the child's height was between height of child and educational level of the mother. When the mother's educational level was below the median for the sample of mothers studied, the likelihood was greater that her child would be short, and conversely if her educational level was above the population median, there was a strong likelihood that her child would be in the taller segment of the population. Our contention at present is that father's education acts mainly though mother's education being the latter the significant factor.

Morrow's (33) in a rural village of Central Mexico found a correlation between a child's diet scale score and mother's education, clearly indicating the importance of women's education in determining food habits.

Review of Previous Studies where Food Scales Have Been Developed

It has not been until recently that several attempts to utilize the methods and techniques of social sciences in the field of nutrition have been made.

In 1951 Abell used the scale analysis in a study of the differential adoption of homemaking practices (42). Using the "Basic Seven" food groups as her guide in a study of rural New York State women, she developed a food scale which ordered the various seven food groups from the lowest to highest frequency. The development of a Guttman scale enabled her to rank the homemakers in five mutually exclusive groups, the five steps of her food scale. She could then compare each of the five groups with various sociological indicators to see whether they differed and where.

Frank W. Young and Andree van Veen have promoted a series of studies that have led to the development of food scales for two regions of Mexico and one of Peru.

With the data collected in four Mexican villages Chassy (43) constructed in 1965 the first scale, and Morrow (33) in 1966 developed a similar type of food scale for another village located in a different geographical region of the country. These two scales showed a number of differences which pointed out the possibility of using this method of food consumption analysis for the patterning of a larger region in a country or for the purpose of cross-cultural comparison.

In Peru, Ahmed (44), using the same methodological principles of Chassy and Morrow has constructed a food scale which correlated to a high degree of statistical significance with a number of socio-economic indicators of increasing complexity, perhaps indicative of modernizing attitudes and practices.

OVERVIEW: the review of the available literature leads to at least the following conclusions.

(*a*) Infant feeding practices are conditioned mainly by social and cultural factors.

(*b*) The economic factors, particularly a low familial purchasing power tends to accentuate the protein and nutrient shortage in this vulnerable group.

(*c*) Malnutrition in the young child is by no means a medical issue only, since over and above the fact that the economy of the family sets the upper limit to the child's food intake, there are numerous ecologic forces intervening in the situation.

(*d*) Except for Mexico and Guatemala, the information about other Latin American countries is very scanty. It is thus felt that more research is needed to document infant feeding practices and recent trends, possible causes of failure of breast-feeding, modifications of maternal diets in pregnancy and lactation, ways to improve nutrition education of the lactating mothers and other relevant research problems, if advances are to be made through sound approaches to improve the nutrition of mothers and their children.

health can afford the luxury of eating what he wants or can afford As a consequence of these beliefs about the relationship of food to health, illness leads to the withdrawal of foods deemed to be in conflict with the disequilibrium of the body which is thought to produce the illness.

The pattern of feeding practices described by Solien and Scrimshaw (38) in a Guatemalan village seems to agree with Foster's observations They report that people in this village fed their children well " not to make them healthy but because they are healthy" A good appetite is associated with health however a child is not forced to eat a food if he resists since his likes and dislikes are respected. Almost any degree of sickness " results with the withdrawal of part of the food from his diet"

Health values cited above as the reasoning behind some food and feeding habits in Latin America are not always the rationales for the decisions In Burgess and Dean's book (34) we have reported observations that cow's milk sometimes is not given to small children because the mother or grandmother has seen that it caused diarrhea The observation of diarrhea following milk consumption appears to be valid in this Mexican community but the mother did not know that the bacterial contamination of the milk was the agent and not the milk per se

In a report on feeding in rural areas (39) we have argued on the basis of our studies that the families through empirical reasoning, in the absence of knowledge on the microbian theory of disease have established their own relationship of cause effect between certain foods and diseases with the unfortunate consequence that it is precisely those foods of high protein value the ones which are said to be harmful to small children which must be omitted from the diet. This fear of food" is the result of careful observations registered through several generations, and a list of harmful foods is passed on from mother to daughter as part of the knowledge and practice of nutrition education"

Food restrictions may also be related to non-modern-scientific concepts of body physiology Huenemann (1) reports the belief in Peru that the child's stomach is not fully formed during the first year and thus cannot handle certain foods. Nevertheless the appropriateness, of various foods and the time at which they are first offered vary greatly with each individual. Most mothers studied by Huenemann had no clear concept of those foods which were good and those which were bad for children in general but rather seemed to depend on individual experiences. Neither was there a concept of special needs for the young child normally he was offered the same foods as the rest of the family after about one year

Ethical concepts may also play a role. The ideas that a person or group has about the whole environment (cosmic ideology shaping food theories and practices) are important as far as food habits are concerned because they may also extend to the ethical field. In this respect Burgess (34) reports that in Thailand frugality is a virtue Young children are brought up to take only the smallest quantity sufficient to flavor the rice of the protein containing side-dish. Greediness with this dish earns strong disapproval, undiminished even where economic necessity does not exist.

Ecological factors and their association with nutritional status of children have been explored over the past 10 years by our research group (3 4 40) through a theoretical framework that divides the amount and quality of the food consumed by the families into two groups The first concerned with the purchasing power of the family and the second covers those factors directly related to the acceptance or refusal of foodstuffs for cultural or psychological reasons and concepts, knowledge and practices directly bearing on the sanitary handling of foodstuffs. Within this conceptualization, there is also a strong interest to explore the educational background, literacy and schooling of the parents, and the use of such communication media as books, radio and newspapers In the study of a Mexican village

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(e) Finally it also seems evident from this review that breast milk is the principal source of protein both on a personal and a community basis for the young child a prolonged breast feeding is still the common practice in rural developing areas. Yet if the world trend away from breast feeding continues the nutritional status of young children instead of improving may deteriorate in the future

THE PRESENT STUDY METHOD AND PROCEDURE

A The Respondents

A purposive" sample of one hundred and twenty five mothers was surveyed by personal interviews. The basic assumption behind purposive sampling was that with good judgement and appropriate strategy one could develop a sample that was satisfactory in relation to one s needs and relevancy of the dimensions to be studied These advantages may outweigh the risks involved in not using probability sampling.

The strategy followed in this purposive sample was that with the knowledge already obtained through ten years of cross-sectional studies of this area it was possible to select cases that were judged to be typical of the population in which one was interested assuming that errors of judgement in the selection will tend to counterbalance each other

It is not usual in a field research study to obtain a sample providing all of the actual parameters to be evaluated Probability sampling procedure for this particular study might have presented a group that would have been inaccessible to systematic observation or interviewing, or a group of such nature that measurement and evaluation would have been impossible If feeding practices and weaning habits were to be studied during the first months of life, if attitudes and beliefs of these women toward diets during pregnancy and lactation were to be explored it follows that these features could only be studied by including in our sample women who had children less than twelve months of age Thus it seems that obtaining a purposive sample—even at the risk of being non representative of the whole village—was in this case an actual requirement of the study

Moreover it must be recognized that the purposive sample s chief defect is not the possibility that it might be in greater error than the probability sample Its real defect is that one can never really calculate just how great the error is (45) It is felt that we were fortunate in this field research to study firstly a sufficiently valid group for the purposes at issue, and secondly to study a relatively large group of mothers in this community that could meet the criteria for including them in the sample

The sample was drawn from a larger group of mothers whose children are being studied longitudinally and included mothers of different ages (ranging from 16 years old to 40 years old or more) of different income levels, of diverse educational background, newcomers to the village as well as old residents etc Complete information on the family and child's record from birth to six months of age was another criterion for including the family in the sample as many of the general background and social variables were to be derived from this data.

B The Instruments

Several instruments were employed in the collection of the data (Appendix shows the English version of the instruments) These were to collect information on

1 Family composition and background data
2 Sanitary facilities available in the home
3 Mother s personal cleanliness
4 Literacy and use of communication media
5 Visiting pattern
6 Child s daily food consumption data
7 Nutrition questionnaire.

All these instruments have been designed pretested and employed by our research team

in other rural areas of similar characteristics. Except for the nutrition questionnaire which was *administered only* once to the mothers all *other data deriving from* the first six instruments were systematically collected and registered over a six month period. Since all the other instruments have been discussed in an earlier publication (41) the nutrition questionnaire and the nature of its format will be the only instrument discussed here.

The purpose of the questionnaire was mainly to assess infant feeding practices since birth to weaning time, nutritional concepts and attitudes, the prevailing food ideology in health and sickness, and in pregnancy *postpartum* and lactation periods, and the actual food consumption of the family in the light and context of other existing socio-cultural correlates. It was *felt that such ambitious aims could only* be accomplished through the use of open-ended questions.

Characteristics pros and cons of the open-ended questionnaire

The distinguishing characteristic of open-ended questions is that *they* merely raise an issue, but do not provide or suggest any structure for the respondent's reply The respondent is given the opportunity to answer in his own terms and in his own frame of reference (45)

From our point of view the *main reason for* our preference for such a format in these types of studies lies in the fact that whatever the design of the research, raw data may lead to important new insights. These may bear on the course of the analysis and may hopefully help to make clear the nature of the relationships among variables. Moreover the examination of this non-quantified, unstructured data may contain clues to the understanding *of* other relevant dimensions, yet unknown, of the frame *of reference in* which the respondent perceives some of the processes under study of the factors that are salient for him, or even of the motivations that underline his opinions.

Two specific and *more* compelling reasons led us to make *the choice of this* format. We wanted questions designed to obtain the *reasons* or *rationalizations* that the mother was going to offer for her food beliefs or habits. In effect, we were *interested in finding out* the why's" *It may seem* like a simple question, but the answers we got were seldom simple. The method used made possible the identification of certain broad classes of considerations or entities *that are likely* to *enter* into the determination of the why's"

An example will serve to illustrate a case in point. The mother was asked which foods she restricted, if any during the post-partum period, and for how long. (See Appendix. Form 3.6 Nutrition Questionnaire.) Then she was asked the reasons for not eating them. Count less reasons were offered by these women, ex pressed in diverse *forms* and *meanings*, with different connotations etc. Yet, after coding and analysis of the raw data, they seem to fall into the following categories.

Magical reasons. (Concepts of "hot" and cold" foods were prevalent in this group See Section on Food Habits and Folk Medicine for an explanation of these concepts.) Ex ample: *Mothers* restricted *fruit*, vegetables and red beans from the diet because those were cold" foods, while consumption of black beans was higher in that period because these were considered hot

Empirical reasons. (Concept of a phenome non being present when another one is present, and of being absent when another one is absent, without the magic" or modern scientific causal *relationship* idea.) Example: *If* she ate pork meat during post-partum period, she would get stomach ache She did not know why "

Modern scientific or contemporary reasons. (Concept of foods as source *of nutrients.*) Ex ample: she did not restrict her food intake because she was suckling her child and needed the *food* to build more strength and produce more breast milk."

Other mothers expressed reasons that seem to fall in two role-playing categories:

(e) Finally it also seems evident from this review that breast milk is the principal source of protein both on a personal and a community basis for the young child, a prolonged breast feeding is still *the common practice in* rural developing areas Yet, if the world trend away from breast feeding continues, the nutritional status of young children instead of improving may deteriorate in the future

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(e) Finally it also seems evident from this review that breast milk is the principal source of protein, both on a personal and a community basis for the young child, a prolonged breast feeding is still the common practice in rural developing areas Yet if the world trend away from breast feeding continues the nutritional status of young children instead of improving may deteriorate in the future

THE PRESENT STUDY METHOD AND PROCEDURE

A The Respondents

A purposive" sample of one hundred and twenty five mothers was surveyed by personal interviews The basic assumption behind purposive sampling was that with good judgement and appropriate strategy one could develop a sample that was satisfactory in relation to one s needs and relevancy of the dimensions to be studied These advantages may outweigh the risks involved in not using probability sampling.

The strategy followed in this purposive sample was that with the knowledge already obtained through ten years of cross-sectional studies of this area it was possible to select cases that were judged to be typical of the population in which one was interested assuming that errors of judgement in the selection will tend to counterbalance each other

It is not usual in a field research study to obtain a sample providing all of the actual parameters to be evaluated Probability sampling procedure for this particular study might have presented a group that would have been inaccessible to systematic observation or interviewing, or a group of such nature that measurement and evaluation would have been impossible If feeding practices and weaning habits were to be studied during the first months of life if attitudes and beliefs of these women toward diets during pregnancy and lactation were to be explored it follows that these features could only be studied by including in our sample women who had children less than twelve months of age. Thus, it seems that obtaining a purposive sample—even at the risk of being non-representative of the whole village—was in this case an actual requirement of the study

Moreover it must be recognized that the *purposive sample s chief defect is not the possibility that it might be in greater error than the probability sample.* Its real defect is that one can never really calculate just how great the error is (45) It is felt that we were fortunate in this field research to study firstly a sufficiently valid group for the purposes at issue and secondly to study a relatively large group of mothers in this community that could meet the criteria for including them in the sample.

The sample was drawn from a larger group of mothers whose children are being studied longitudinally and included mothers of different ages (ranging from 16 years old to 40 years old or more) of different income levels, of diverse educational background, newcomers to the village as well as old residents, etc Complete information on the family and child's record from birth to six months of age was another criterion for including the family in the sample as many of the general background and social variables were to be derived from this data.

B The Instruments

Several instruments were employed in the collection of the data (Appendix shows the English version of the instruments) These were to collect information on

1 Family composition and background data
2 Sanitary facilities available in the home
3 Mother s personal cleanliness
4 Literacy and use of communication media
5 Visiting pattern
6 Child s daily food consumption data
7 Nutrition questionnaire

All these instruments have been designed, pretested and employed by our research team

in other rural areas of similar characteristics. Except for the nutrition questionnaire which was administered only once to the mothers all other data deriving from the first six instruments were systematically collected and registered over a six-month period. Since all the other instruments have been discussed in an earlier publication (41) the nutrition questionnaire and the nature of its format will be the only instrument discussed here.

The purpose of the questionnaire was mainly to assess infant feeding practices since birth to weaning time, nutritional concepts and attitudes, the prevailing food ideology in health and sickness, and in pregnancy postpartum and lactation periods, and the actual food consumption of the family in the light and context of other existing socio-cultural correlates. It was felt that such ambitious aims could only be accomplished through the use of open-ended questions.

Characteristics pros and cons of the open-ended questionnaire

The distinguishing characteristic of open-ended questions is that they merely raise an issue, but do not provide or suggest any structure for the respondent's reply. The respondent is given the opportunity to answer in his own terms and in his own frame of reference (45).

From our point of view the main reason for our preference for such a format in these types of studies lies in the fact that whatever the design of the research, raw data may lead to important new insights. These may bear on the course of the analysis and may hopefully help to make clear the nature of the relationships among variables. Moreover the examination of this non-quantified, unstructured data may contain clues to the understanding of other relevant dimensions, yet unknown, of the frame of reference in which the respondent perceives some of the processes under study of the factors that are salient for him, or even of the motivations that underline his opinions.

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Reasons denoting a more *passive* role (Acceptance of the eating pattern without awareness or questioning.) Example She just ate whatever her mother in-law allowed her to eat in that particular period or she was taught to eat only such foods or this was what she was given when she had her first child so she continued that custom etc

Reasons that denoted a more *active* role (Active participation in the decision—making process of food selection likes and dislikes.) Example She ate what ever she felt like eating or happened to have at home during that period" or "she not only ate what the midwife recommended, but she would ask for other foods.

In addition to the reasons for a given belief or action pattern the why s" could also provide us with relevant insight into the *reasons for alternative beliefs or actions* even in spotting the deviant cases For example it was noticed that although few in number there were some mothers who were following a different eating pattern during the post partum period These mothers did not eliminate any foods from their regular diet, but rather consumed their regular basic meals plus additional food items such as vegetables and fruits which normally would not be included by the majority of the women When asked the reasons for following such a practice they reported that by having delivered their child at a hospital or a clinic they were compelled to eat regularly a meal which included fruit and vegetables Thus in the hospital they were exposed for the first time to eat a different meal and afterwards they were not so afraid to follow the new eating pattern at home when they had subsequent pregnancies

The above example illustrates the role probably played by a social institution in altering or modifying the mother s eating pattern. If the association holds to be true it becomes of paramount importance for nutrition education purposes and was only possible to explore because of the nature and format of the open ended questionnaire

In spite of all the advantages just discussed, the open-ended questionnaire is difficult, expensive and time-consuming to analyze. Categories for analysis must be built up for which a balance of theoretical as well as empirical considerations must prevail. Coders must also be trained All responses must be recorded individually and then coded into one of the categories before they can be tabulated and statistically analyzed

In short, compared to the simple process of tabulating pre-coded responses to closed questions the analysis of an open-ended questionnaire is a complex process, but as has previously been emphasized the nature of the research problem should be the major determinant of the instrument s format

C The Interview

One of the authors conducted all the interviews necessary to complete the nutrition questionnaire so variation of personalities or interviewers affecting or biasing the measurement situation was avoided and consequently ensured some uniformity of standard wording and phrasing of the questions. In cases where questions were not understood by the mothers, help to understand the question was provided by repeating or rephrasing it in a more meaningful way

Two possible drawbacks of this type of interview must be pointed out First, the excessive length of time demanded from the informants. The interview itself lasted from one-and half to two hours each depending on the mother s ability to verbalize her opinions or responses, even though it did not seem to bother them or handicap the collection of the data Secondly the format of the questionnaire itself required extended written responses which the interviewer had to write fully as respondents were speaking, with the possibility of some loss of information Because of the excellent assistance and friendly attitude shown by the mothers, again this did not seem to impose great limitations on the data gathering.

D The Data as Part of a Longitudinal Study to Explore the Effects of Malnutrition on Mental Development

The fact that much of the information used in this study was collected as part of a longitudinal field research is in itself considered an asset.

The information on the general background and composition of the families, communication, health and social variables was obtained and recorded by social workers living in the village. The infant food intake data is the product of a systematic and careful recording performed by trained personnel through weekly home visits, during a period of six months. The advantage seems remarkable when contrasted with other food intake studies where the data has been collected either during a period of twenty-four hours, or a three-day survey where biases are likely to occur with possible contamination" of the results because of the narrow range period of the study or the day-to-day seasonal variations in the food intake. It seems reasonable then to assume that these data systematically recorded over this prolonged period allows greater confidence and reliability in the findings.

The family was chosen as the unit of analysis. The data covers a wide range of information which could fall into broad dimensions, such as.

Health variables
mother's number of pregnancies
place of delivery
delivery attendance (M.D Midwife)
housing conditions
mother's personal hygiene
weaning time

Education variables
father's occupation
mother's education

Social variables
father's occupation
mother's social orientation (traditional, modern)
mother's social participation (visiting pattern)

Communication variables
father's reading newspaper
father's listening to the radio
father's watching TV
mother's reading newspaper
mother's listening to the radio
mother's watching TV

General background variables
family size and composition
father's age
mother's age

Food variables
infant food introduction scale
family food consumption scale

Much of the data also covers the attitudes and concepts of the mother toward breast-feeding practices and weaning habits, food beliefs, etc. of immediate interest to this analysis.

Coding the data

All the information collected was transferred to IBM standard cards (80 columns by 12 rows) for use with data processing equipment. In regard to the nutrition questionnaire all possible replies were tabulated on a rough matrix in order to make possible clusters" of categories. Each of these categories was then assigned a number from 0 to 9 consecutively. All such assignments for all questions carefully recorded constituted the code. Most of the data were also coded in rank order as this was to be a precondition for the tests of association demanding ordinal ranking.

Operationalizing the variables

(1) *Social variables.* Occupation is grouped according to the primary source of income of the father which comprise the following five categories, interpreted as an ordinal measure: agricultural (peón) day laborer (ejidatario) family plot owner (*arrendatario*) land renter small land owner craftsman or professional.

The social participation of the mother was operationally defined as the number of outside contacts and visiting recorded during a six

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Respondent	Key no.	Food items								Score
		1	2	3	4	5	6	7	8	
O. Garcia	001	1	0	1	1	1	0	1	0	5
C. Pérez	002	1	0	0	0	1	0	1	1	4
D. Avila	003	1	1	0	0	1	0	1	1	5
B. Ibarra	004	0	0	0	0	1	0	1	0	2
Z. Lasso	005	1	0	0	0	1	0	1	0	3
Q. Pinto	006	1	0	0	0	1	0	1	1	4
M. Vega	007	1	1	0	1	1	1	1	1	7
E. Chen	008	1	0	0	1	1	0	1	0	4
D. Ortiz	009	1	1	0	1	1	1	1	1	7
S. Rojas	010	1	1	0	1	1	0	1	1	6

Note that we have given each respondent a score equal to the number of *Yes* answers she has given.

Let us now rearrange the table, by placing the *rows* (respondents) in order of their scale score. The result is shown in the following table.

Respondent	Key no.	Food items								Score
		1	2	3	4	5	6	7	8	
	007	1	1	0	1	1	1	1	1	7
	009	1	1	0	1	1	1	1	1	7
	010	1	1	0	1	1	0	1	1	6
	001	1	0	1	1	1	0	1	0	5
	003	1	1	0	0	1	0	1	1	5
	002	1	0	0	0	1	0	1	1	4
	006	1	0	0	0	1	0	1	1	4
	008	1	0	0	1	1	0	1	0	4
	005	1	0	0	0	1	0	1	0	3
	004	0	0	0	0	1	0	1	0	2

Finally let us rearrange the *columns* (food items) in the table, by putting them in order of the number of Yes (1) answers given to each time, as shown in the next table.

Respondent	Key no.	Food items								Score
		7	5	1	2	4	8	6	3	
	007	1	1	1	1	1	1	1	0	7
	009	1	1	1	1	1	1	1	0	7
	010	1	1	1	1	1	1	0	0	6
	001	1	1	1	0	1	0	0	1	5
	003	1	1	1	1	0	1	0	0	5
	002	1	1	1	0	0	1	0	0	4
	006	1	1	1	0	0	1	0	0	4
	008	1	1	1	0	1	0	0	0	4
	005	1	1	1	0	0	0	0	0	3
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A scalogram pattern with high reproducibility has been produced. Knowing a respondent's score (or scale step position) enables one to know her responses to all eight items. A score of 3 clearly means a Yes-response to items 7,5 and 1 a score of 6 means a Yes-response to items 7 5 1 2, 4 and 8, and so on. The lowest item on the scale is 7 which everyone consumed, the highest or most discriminating one is item 3 which almost no one consumed.

The former example has been used to illustrate the technique of Guttman scale construction. In practice, one may have to rearrange the order of items and or respondents, not once or twice, but many times until the nearest "fit" or approximation to a scalogram pattern is obtained.

Coefficient of scalability (*C of S*) This coefficient of scalability developed by Menzel (49) can be used to estimate the seriousness of errors that may occur in the scale. Zeros" in a field of Ones" and ones" in a field of zeros" represent errors which are designated by a slash (/) to indicate their being counted (see last scale model).

The use of this coefficient, which runs from 0 to 1 makes it possible to speak meaningfully of degrees of scalability instead of merely deciding whether a set of items scale or not. The acceptance level lies somewhere between 0 60 and 0 65 This coefficient cannot be spuriously raised by combining categories so as to form many extreme items, as it provides an automatic safeguard, inherent in the calculation against this form a misinterpretation. It imposes an exact mathematical penalty for the exact amount of new extremeness created through the combination of categories.

Guttman scales also have a built-in reliability It is a type of reliability which refers to performance of a particular set of items at a particular moment in time " (50) Thus, the estimates of reliability of these scales have been obtained through the analysis of the consistency of response to individual food

month period Travels to Mexico City or nearby towns or villages, visits to relatives and friends, church attendance or visits to health center market place etc It can be noted that the items included in this index attempt to measure both urban contacts as well as neighborhood visiting.

The social orientation of the mother is scored in relation to her food beliefs in different healthy and sick states.

(2) *Health variables* Delivery attendance refers to the assistance at the birth of the last child Housing conditions refers to a house sanitation index arrived at after scoring different objective sanitary facilities or elements available at home such as type of floors, type of walls, presence of animals and vectors of disease, crowding of adults and children, etc Mother s personal hygiene also represents a cumulative score (Score see Forms 1 4 and 1.5 Appendix A) Weaning time refers to the length (in months) of breast feeding of the youngest child.

(3) *Communication variables* These variables were dichotomized for yes" and no" with respect to use of such communication media as books, radio, newspaper reading, and television watching.

(4) *Food variables* Both the infant and family food scales developed constitute the two dependent variables in this study The data for the development of the family food scale came from a one-day food intake taken during the different days of the week thus allowing for week-days variation in food consumption Each food item was dichotomized for presence or absence in that particular day s meals

Methods of Treatment of the Data

1 Scalogram analysis

Scalability is a certain pattern of responses on the part of a given number of individuals to a given set of items (46) The primary quality of the Guttman scale or scalogram is that of *unidimensionality* or the measurement of a single concept in an ordinal and cumulative way

The scalogram hypothesis is that the items (variables) have an order such that, ideally persons who answer a given question favorably will have higher ranks than persons who answer the same question unfavorably " (47) Knowing the items, a person s responses to a set of items in a scale can be known simply by knowing how many items he answered favorably This property of *reproducibility* of answers from knowledge of score is another fundamental characteristic of the Guttman scale

The procedures of scalogram analysis are designed to test a given universe of content, or at any rate a group of items for scalability" by seeing whether it will yield a scale with a satisfactory coefficient of reproducibility Actually not all areas of content will scale especially not if they are wide and heterogeneous, and one cannot know beforehand whether the attempt at scale construction will be successful. The procedure has been criticized for this and for a tendency to produce scales covering a very narrow universe of content because wider areas do not often scale (48)

To illustrate the above theoretical considerations of this method let us assume we start out with a set of food items and that we have obtained these (as yet unscaled) items from our one hundred and twenty five mothers interviewed. This group of food items is used to index the concept in this particular study the underlying concept of food complexity The food items may be thought of as steps in a cumulative progression, from simple to complex eating patterns. The items have been previously dichotomized in function of their consumption—Yes (1) or No (0). A tabulation of the results for the first ten cases might look like the following

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	010	1	1	0	1	1	0	1	1	6
	001	1	0	1	1	1	0	1	0	5
	003	1	1	0	0	1	0	1	1	5
	002	1	0	0	0	1	0	1	1	4
	006	1	0	0	0	1	0	1	1	4
	008	1	0	0	1	1	0	1	0	4
	005	1	0	0	0	1	0	1	0	3
	004	0	0	0	0	1	0	1	0	2

Finally let us rearrange the *columns* (food items) in the table, by putting them in order of the number of Yes (1) answers given to each time, as shown in the next table.

Respondent	Key no.	Food items 7	5	1	2	4	8	6	3	Score
	007	1	1	1	1	1	1	1	0	7
	009	1	1	1	1	1	1	1	0	7
	010	1	1	1	1	1	1	0	0	6
	001	1	1	1	[illegible]	1	0	0	1	5
	003	1	1	1	1	0	1	0	0	5
	002	1	1	1	0	0	1	0	0	4
	006	1	1	1	0	0	1	0	0	4
	008	1	1	1	0	1	0	0	0	4
	005	1	1	1	0	0	0	0	0	3
	004	1	1	0	0	0	0	0	0	2

A scalogram pattern with high reproducibility has been produced. Knowing a respondent's score (or scale step position) enables one to know her responses to all eight items. A *score* of 3 clearly means a Yes-response to items 7,5 and 1 a score of 6 means a Yes-response to items 7 5 1 2, 4 and 8, and so on. The lowest item on the scale is 7 which everyone consumed, the highest or most discriminating one is item 3 which almost no one consumed.

The former example has been used to illustrate the technique of Guttman scale construction. In practice, one may have to rearrange the order of items and or respondents, not once or twice, but many times until the nearest fit or approximation to a scalogram pattern is obtained.

Coefficient of scalability (C of S) This coefficient of scalability developed by Menzel (49) can be used to estimate the seriousness of errors that may occur in the scale. Zeros" in a field of Ones and ones" in a field of zeros represent errors which are designated by a slash (/) to indicate their being counted (see last scale model).

The use of this coefficient, which runs from *0 to 1 makes it possible to speak meaningfully* of degrees of scalability instead of merely deciding whether a set of items scale or not. The acceptance level lies *somewhere* between 0 60 and 0 65 This coefficient *cannot* be spuriously raised by combining categories so as to form many extreme items, as it *provides* an automatic safeguard, inherent in the calculation against this form a misinterpretation. *It* imposes an exact mathematical penalty for the exact amount of new extremeness created *through* the combination of categories.

Guttman scales also have a built-in reliability It is a type of reliability which refers to

performance of a particular set of items at a particular moment in time (50)

Thus, the estimates of reliability of these scales have been obtained through the analysis of the consistency of response to *individual food*

month period Travels to Mexico City or nearby towns or villages, visits to relatives and friends, church attendance or visits to health center market place etc It can be noted that the items included in this index *attempt to* measure both urban contacts as well as neighborhood visiting.

The social orientation of the mother is scored in relation to her food beliefs in different healthy and sick states

(2) *Health variables* Delivery attendance refers to the assistance at the birth of the last child. Housing conditions refers to a house sanitation index arrived at after scoring different objective sanitary facilities or elements available at home such as type of floors, type of walls, presence of animals and vectors of disease crowding of adults and children, etc Mother's personal hygiene also represents a cumulative score (Score see Forms 1 4 and 1.5 Appendix A.) Weaning time refers to the length (in months) of breast feeding of the youngest child.

(3) *Communication variables* These variables were dichotomized for yes" and no" with respect to use of such communication media as books, radio newspaper reading, and television watching.

(4) *Food variables* Both the infant and family food scales developed constitute the two dependent variables in this study The data for the development of the family food scale came from a one-day food intake taken during the different days of the week thus allowing for week-days variation in food consumption Each food item was dichotomized for presence or absence in that particular day's meals.

Methods of Treatment of the Data

I Scalogram analysis

Scalability is a certain pattern of responses, on the part of a given number of individuals, to a given set of items (46) The primary quality of the Guttman scale or scalogram *is that of unidimensionality* or the measurement of a single concept in an ordinal and cumulative way

The scalogram hypothesis is that the items (variables) have an order such that, ideally persons who answer a given question favorably will have higher ranks than persons who answer the same question unfavorably " (47) Knowing the items a person's responses to a set of items in a scale can be known simply by knowing how many items he answered *favorably* This property of *reproducibility* of answers from knowledge of score is another fundamental characteristic of the Guttman scale

The procedures of scalogram analysis are designed to test a given universe of content, or at any rate a group of items for scalability" by seeing whether it will yield a scale with a satisfactory coefficient of reproducibility Actually not all areas of content will scale especially not if they are wide and heterogeneous, and one cannot know beforehand whether the attempt at scale construction will be successful. The procedure has been criticized for this and for a tendency to produce scales covering a very narrow universe of content because wider areas do not often scale (48)

To illustrate the above theoretical considerations of this method, let us assume we start out with a set of food items and that we have obtained these (as yet unscaled) items from our one hundred and twenty five mothers interviewed. This group of food items is used to index the concept in this particular study the underlying concept of food complexity The food items may be thought of as steps in a cumulative progression, from simple to complex eating patterns The items have been previously dichotomized in function of their consumption—Yes (1) or No (0) A tabulation of the results for the first ten cases might look like the following:

Respondent	Key no.	Food items								Score
		1	2	3	4	5	6	7	8	
O. García	001	1	0	1	1	1	0	1	0	5
C. Pérez	002	1	0	0	0	1	0	1	1	4
D. A[illegible]la	003	1	1	0	0	1	0	1	1	5
B. Ibarra	004	0	0	0	0	1	0	1	0	2
Z. Lasso	005	1	0	0	0	1	0	1	0	3
Q. Prato	006	1	0	0	0	1	0	1	1	4
M. Vega	007	1	1	0	1	1	1	1	1	7
E. Chan	008	1	0	0	1	1	0	1	0	4
D. Ortiz	009	1	1	0	1	1	1	1	1	7
S. Rojas	010	1	1	0	1	1	0	1	1	6

Note that we have given each respondent a score equal to the number of *Yes* answers she has given.

Let us now rearrange the table, by placing the *rows* (respondents) in order of their scale score. The result is shown in the following table.

Respondent	Key no.	Food items								Score
		1	2	3	4	5	6	7	8	
	007	1	1	0	1	1	1	1	1	7
	009	1	1	0	1	1	1	1	1	7
	010	1	1	0	1	1	0	1	1	6
	001	1	0	1	1	1	0	1	0	5
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	006	1	0	0	0	1	0	1	1	4
	008	1	0	0	1	1	0	1	0	4
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Respondent	Key no.	Food items								Score
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	001	1	1	1	0	1	0	0	1	5
	003	1	1	1	1	0	1	0	0	5
	002	1	1	1	0	0	1	0	0	4
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The gamma" test developed by Goodman and Kruskal (46) is described by Costner (51) as falling into the group of measures involving the mechanical application of the product moment formula to ordinal data The test assumes a cross-classification of attributes, given a set of bivariate observations, each represented by a set of *ordered classes* This measure is essentially based on predicting the *direction of the order* and how consistently this order is reproduced. If there is any association between variables A and B we ought consistently to get either "like" orders (representing positive association) or unlike" orders (representing negative association) And if there is no association we get neither consistently like following unlike order more or less at random.

In short a gamma coefficient goes from −1 to +1 and tells how much more probable a like order is than an unlike order

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Results obtained are of two types First, a descriptive analysis of maternal nutrition, infant feeding practices and weaning habits which will be discussed together with associated variables. And second the development of two food scales representing increasing levels of dietary complexity which will be discussed as they relate to some social and health correlates.

A Maternal and Infant Nutrition

Because of their interdependence maternal and infant nutrition practices will be discussed here jointly Up to what extent one relates to the other and up to what degree the beliefs and practices of the mother affect the infant will be of major and immediate interest to this study A descriptive analysis within a cultural framework will initiate this discussion, looking at the child from the neonatal period up to his preliminary participation into the family s regular meal pattern

Before delivery a pregnant woman does not eat special foods to nourish her baby or strengthen herself Ninety per cent of the mothers reported no modifications of their regular diet when questioned about the ingestion of special foods during pregnancy

Before birth the mother does nothing to prepare her breasts for nursing. In eighty six per cent of the cases, the child is born at home and the mother is assisted in delivery by a female midwife and some relatives. Table 1 presents

a cross-tabulation of place of delivery of child by father's occupation. In comparing the per centages across the table *no meaningful* differ ences are found among the lower and the higher occupations of the father The low cor relation coefficient found may lead us to as-sume that the economic factor was not the ma-jor determinant in the choice of place of deliv ery of the child.

Table 1 *Relationship between father's occupation and place of delivery*

Correlation coefficient = 0.18. Figures in parenthesis correspond to number of infants

Place of delivery	Father's occupation 1	2	3	4	5	0		
	Percentage of infants							
Home	89	70	89	(1)	83	86		(105)
Hospital	10	30	11	—	17	14		(16)
	(7)	(72)	(10)	(1)	(24)	(7)	N	(121)

Code for father' occupation:
1 Agricultural day laborer
2. Family plot owner
3. Land renter
4 Small landowner
5. Craftsman or professional
0. No information

I Breast Feeding

Neonates are not nursed until the second day (22% of the cases) or third day (49% of the cases) because the mother considers colostrum unfit *for the child as claimed by* 14% of the mothers, or because as 38% of the cases re-ported, the milk does not come down until after the third day" Consequently herb teas were given to the neonate. As many as twelve different kinds of teas were reported by the mothers, which included among them *yerba-buena* (spearmint) and *manzanilla*, as the most common ones, followed by cinnamon, *orégano rosa de castilla*, *anis* lemon and orange leaves, etc. These teas are also thought to have remedial effects (13% of the cases) and are popularly recommended by midwifes, mothers-in-law and grandmothers to cure *cólico* or stomach ache.

Breast-feeding by the third day is normally routine (87% of the cases), but if lactation does not begin by then, one of a wide variety of techniques to induce it may be adopted. Women have recourse to traditional methods which are believed to ensure an abundant flow of milk These generally include drinking liq-uids of various kinds, such as *atoles* (cereal gruels)

This beverage, when made out of legumes *such as ajonjoli* or groundnuts, is thought to have great value as a galactogogue Consump-tion of fish or meat broth, or of a chocolate drink made with cocoa, sugar and milk, is also frequently reported. *Sea-foods, particularly* fish, are favorites because of their *supposed* milk-making properties. Some mothers also mentioned taking yeast pills as the last resort to induce lactation. Sixty-five per cent of the mothers however agreed that strong" foods, such as wheat bread and drinking of milk and broths, were the best ways to promote lacta-tion.

Permanent lactation failure was reported only by one mother although 14% agreed that the *higher* the number of pregnancies the less the milk output.

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Most mothers had no troubles in the early months of breast-feeding, although 41% com-plained of swollen breasts and nipples.

To assess the attitude toward communal" feeding, mothers were asked if they would al-low the child to be nursed by a woman who was not his mother Thirty-five per cent of the mothers reported their willingness to accept this *practice if, for a few days*, the natural mother could *not feed her child because of*

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The tables will present the hypothetical independent variable *percentaged down* so that percentage difference comparisons should be made comparing across, in function of the row (dependent) variable A correlation coefficient has also been computed and will be shown for each cross tabulation, as to provide a second and stronger measure for the interpretation of each table

3 The "gamma test of association

The gamma" test developed by Goodman and Kruskal (46) is described by Costner (51) as falling into the group of measures involving the mechanical application of the product moment formula to ordinal data. The test assumes a cross-classification of attributes, given a set of bivariate observations, each represented by a set of *ordered classes* This measure is essentially based on predicting the *direction of the order* and how consistently this order is reproduced If there is any association between variables A and B we ought consistently to get either like" orders (representing positive association) or unlike" orders (representing negative association) And if there is no association we get neither consistently like following unlike order more or less at random.

In short a gamma coefficient goes from − 1 to + 1 and tells how much more probable a like order is than an unlike order

RESULTS AND DISCUSSION

Results obtained are of two types First, a descriptive analysis of maternal nutrition infant feeding practices and weaning habits which will be discussed together with associated variables. And second, the development of two food scales representing increasing levels of dietary complexity which will be discussed as they relate to some social and health correlates

A Maternal and Infant Nutrition

Because of their interdependence maternal and infant nutrition practices will be discussed here jointly Up to what extent one relates to the other and up to what degree the beliefs and practices of the mother affect the infant will be of major and immediate interest to this study A descriptive analysis within a cultural framework will initiate this discussion, looking at the child from the neonatal period up to his preliminary participation into the family's regular meal pattern.

Before delivery a pregnant woman does not eat special foods to nourish her baby or strengthen herself Ninety per cent of the mothers reported no modifications of their regular diet when questioned about the ingestion of special foods during pregnancy

Before birth the mother does nothing to prepare her breasts for nursing. In eighty-six per cent of the cases, the child is born at home and the mother is assisted in delivery by a female midwife and some relatives. Table 1 presents

2 Supplementary Feeding

Supplementary feeding and the refusal of the breast to the child are generally placed indiscriminately under the term "weaning" The weaning process is a slow one and may be subdivided into several stages: (*a*) the introduction of supplementary foods, (*b*) the refusal of the breast to the child, and (c) the full participation of the child in the family's table-fare

These stages will be examined in that order with particular emphasis on the first two

(*a*) *The introduction of supplementary foods*

An infant food scale with six-scale steps was found as a measure of the unidimensional quality of food complexity being introduced to the child during his first six months of life. Table 3 shows the scale steps and the proportion of infants who had positive responses for each level. For each item a positive response means that the food was introduced and consumed during the six month period.

As one examines the infant food scale, it should be noted that each food scale step represents not only the introduction of another food group, but also indicates the addition of other foods at each higher step in the scale.

The coefficient of scalability of 0 69 obtained is over the acceptable value of 0.65 yet it is not high enough to consider the scale highly reliable as a predictive measure. A coefficient of 0 70 has been previously reported by Morrow (33) in her study of Mexican children in the same village, using cross-sectional food data.

The first two steps of the scale, breast milk and herb teas, form the basis of the diet introduced to the infant during the neonatal period.

The inclusion of herb teas is not surprising in the scale, since it is traditional that herb teas are fed to the child, especially during his early days of life.

In the category of breast milk, there was only one mother who did not suckle her child at all. Coincidentally enough, of all the mothers interviewed she happened to fall in the highest socio-economic strata.

Table 3 *The food scale found for infants at six months of age in the land of the white dust*

Total number of cases = 125. Coefficient of scalability = 0.69

Scale steps	Item content	Infants (%)	No.
1	Breast milk	100	124
2	Herb teas (*Yerbabuena and Manzanilla*)	79	98
3	Other milks (cow's milk, either fresh or powered, goat's milk)	60	75
4	Fruit (mainly banana, orange, apple)	43	54
5	*Caldo de Frijol* (red beans, cooked and mashed into a soup)	41	52
6	*Tortilla* (corn-flat-bread, stappled cereal)	39	49

The third step—"Other Milks"—includes cow's milk, either fresh, in powder or evaporated, as well as goat's milk.

Fruits, *caldo de frijol* (bean soup) and *tortilla* appear to be somewhat less basic in the infant's diet at this particular age period. As milk and fruits (bananas in particular) are considered especially suitable for infants, their presence in the scale was expected These last three steps appear to be highly selective in the percentage of infant population eliminated as the diet increases in complexity It is our feeling that the discriminating factor operating in steps 4 5 and 6 of the scale is not so much food availability since beans and tortillas form the basic dietary pattern of Central Mexico but rather the age of the child and the mother's readiness to introduce these new foods at an early stage this in turn might suggest a rough indication of "differentiation" or a more modernizing attitude toward infant feeding practices.

Bean soup the *fourth* scale step, is usually given mashed as a watery soup, as the whole red bean is not given to the child until later in life.

Fruits include a wide variety mostly tropical, but the ones most commonly mentioned in the *infant's* diet were bananas, followed by oranges, apples, and papaw

Table 2. *Relationship between type of feeding and place of delivery*

Correlation coefficient – 0.23 Figures in parenthesis correspond to number of infants

Type of feeding	Place of delivery		
	Home	Hospital	
	Percentage of infants		
Permissive demand	59	47	(71)
Rigid scheduled feeding	39	47	(50)
Do not know	–	6	(3)
	(107)	(17)	N – (124)

sickness or sudden lactation failure If the mother was away and her child suffered hunger and cried continuously another woman could nurse him This was considered a friendly and neighborly act In one instance a young grand mother (40 years old) who herself was nursing her own child did also nurse her grandchild. The majority of the women interviewed (65 % of the total) would not accept "communal" feeding under any circumstances, and manifested that they would rather turn to early initiation of bottle feeding if they were to experience lactation failure Some remarked "there is nothing like God and one s mother " and others even expressed fear that if the child was nursed by another woman he might not recognize her as his "own" mother at a later time

The initiation of breast feeding is simple Mothers (79) wash their nipples with water and alcohol This practice is dropped once the baby gets older The infant may be fed while the mother is lying down or sitting Forty three per cent of the mothers preferred the sitting position 23 preferred lying down in bed, and 5 % fed their infants both ways. They remarked that either at night, or when the child was very young, they preferred lying down. During the daytime or when the child grew older they chose the sitting position

The infant is generally allowed to suck from both breasts at each feeding (61 % of the cases) for as long as he wishes, or until he falls asleep Another reason for preference of feeding from both breasts (given only by a few mothers) was the fear that if the child was fed from only one breast, this breast will get smaller and the milk will subsequently dry"

Nursing the child is an affectionate action on the mother s part and she is indulgent during the act The infants are fed whenever they cry during the day or during the night, until they are weaned. Fifty-eight per cent of the mothers feed their children on self-demand, and 40 were also in favor of so-called "modern" ideas in feeding behavior i.e., they practiced rigid scheduled feeding. A significant trend was found between place of delivery and type of feeding Delivery of a child at a hospital or clinic increasing the likelihood of rigid schedule feeding (Table 2)

The "modernity" of feeding on a rigid schedule could also be explained in function of the "differentiation" concept. The practice could reflect a more complex thinking in the family unit as is already exemplified by the choice of the place of delivery

In this respect, it is worth pointing out that the current trend favored by child health authorities nowadays is a return to non-scheduled self-demand feeding. This contradiction exemplifies the difficulties experienced by the health educator who after the investment of a lot of time and effort finally achieves a change in the behavior of an important number of individuals just to find at that moment that the previous "wrong" behavior is now scientifically accepted as good and modern. Will he go back and undo what he has done? Perhaps this should be a good point in favor of the slow tempo generally taken by the communities in accepting change and "modernization" The data on feeding practices during the neonatal period, as well as on maternal practices, can be summarized as still showing an attachment to the traditional ways of life, although some "modernizing" trends are beginning to appear This suggests that food and health behavior are dynamic and flexible rather than rigid forces in this community

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The coefficient of scalability of 0.69 obtained is over the acceptable value of 0.65 yet it is not high enough to consider the scale highly reliable as a predictive measure. A coefficient of 0.70 has been previously reported by Morrow (33) in her study of Mexican children in the same village, using cross-sectional food data.

The first two steps of the scale, breast milk and herb teas, form the basis of the diet introduced to the infant during the neonatal period.

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Fruits include a wide variety mostly tropical, but the ones most commonly mentioned in the infant's diet were bananas, followed by oranges, apples, and papaw

Tortilla is fed to children usually mixed with bean soup in order to soften its texture.

The fact that the foods in the infant s diet do form a scale is evidence that an underlying pattern exists associated with their feeding habits. It suggests that rather than a merely random list of foods, the food reports collected over a long period are structured quite consistently With the development of the scale we now also know which individual food groups are included in this dietary pattern.

One implication borne out by the scale is a strong support for the assumption that an infant s dietary pattern does in fact exist in this community On numerous occasions it has been contended that in Latin American rural societies the child is exclusively breast fed during a period of no less than 12–18 months or that no new food is introduced to the child during this period Obviously this is not the case in this village and might not very well be the case for many other Latin American rural areas Scarcity of empirical quantitative studies to support these contentions have sometimes contributed to some of these over simplified generalizations, particularly in the field of infant nutrition

In a latter section of this discussion we will turn our attention to the relationships obtained between the infant food scale and certain social correlates.

Scoring technique for items that did not scale Due to the fact that some of the food items that were most frequently mentioned by the mothers did not scale a scoring technique was introduced into the analysis to take these foods into account, and later on to correlate them with the infant food scale, so as to introduce a validation factor into the data

The following six additional food items were considered for scoring:

1 *Atoles* (gruels)
2 Bread, Crackers, Cookies
3 *Sopa Aguada* (watery noodle like soup)
4 Cocoa or Coffee with Milk
5 Eggs
6 Jello" (flavored gelatin)

Atoles is an item considered suitable for children which we assumed would scale and which did not. Several scaling attempts were tried through reshuffling of cases and columns. In some of these trials atoles was placed in between Other Milks" and Caldo de Frijol" but the resulting coefficients of scalability were not acceptable Likewise, *Sopa aguada* customarily served at noon time, and also thought to be nutritious for children, did not scale. Bread and chocolate drinks also reported as frequently consumed by the infants were excluded from the scale because of greater percentage of errors Eggs were not included because they did not have a very high frequency of use during this early period of the infant s life and so did not scale by themselves, although they did scale in the family food scale to be reported later in this discussion.

The scoring procedure was to assign a score of "1" for each food item present in the infant diet Twelve food items, six from the scale steps and six from the food list, were included, thus rendering 12 as the maximum possible score that could be obtained by a child. The food scores were trichotomized in the categories of High Scores (9 to 12 items), Medium Scores (5 to 8 items) and Low Scores (1 to 4 items) The results of the correlation between food score and infant s position in the food scale are shown in Table 4

As can be noted in the table a significant correlation was found between scale and score. Infants having a high score clustered in the higher steps of the food scale while infants with low scores placed in the lower or medium scale steps. This finding increases the confidence that can be given to the infant food scale as such

(b) Introduction of foods during the first semester of life

Table 5 shows a list of twenty two different food items introduced to this group of infants by the month in which the particular food was introduced As can be observed from the table, there is the widest possible range of foods em-

ployed. In many cases the infants received only small amounts or merely tastes of food, most usually about the age of three to four months.

Pérez-Navarrete's (32) and Morrow's (33) findings for this same community several years before the present study showed later months of introduction of semi-solid foods. In Pérez Navarrete's sample ninety-one per cent of the infants were fully breast-fed at the end of six months while in the present study only nine per cent of the infants were fully breast-fed at the end of this period.

Atoles either prepared with milk or water cinnamon and sugar or chocolate and coffee with milk were among the first foods introduced, apart from the milks and herb teas introduced during the first three days of the infant's life.

Cow's milk is given to children almost always boiled, not necessarily for reasons of hygiene, but because unboiled milk is considered to be "cold" For apparently similar reasons, mothers use cinnamon or lime leaves, chocolate and coffee as flavoring agents for the milk Thus feeding of plain cow's or goat's milk to the child was rarely reported.

By the fourth month most of the twenty-two food items, with the exception of eggs and meats, were already introduced by some mothers.

The broth of the bean soup is usually given to the child, but not the beans as such, as it is believed that they are "heavy" food and that the child cannot tolerate them well. The "goodness" of a food is judged by its digestibility and according to whether or not the

Table 4 *Correlation between infant food scale and infant food scores*

Correlation coefficient 0 70

Food scores	Number of infants in scale steps 1 2	3-4	5-6
Low scores (1-4)	19	16	0
Medium scores (5-8)	7	31	28
High scores (9-12)	1	1	22

Table 5 *Age of introduction by type of food*

Food items	Months 1 (number of infants)	2	3	4	5	6	Total	% of total for row
Breast milk	124	—	—	—	—	—	124	100
Herb teas	96	—	—	1	1	—	98	79
Cow's milk (fresh)[a]	15	6	6	5	5	17	54	43
(powder)[a]	12	6	2	6	1	2	29	23
Goat's milk	—	1	—	—	1	1	3	—
Fruit	2	1	3	8	14	25	54	43
Bean soup	—	—	—	4	14	34	52	41
Atoles	13	7	6	7	11	7	51	41
Tortilla	—	—	—	2	10	37	49	39
Bread, crackers	—	—	—	1	9	34	44	35
Sugar	9	6	4	5	7	6	37	30
Chocolate, coffee	3	1	1	3	6	15	29	23
Sopa aguada	—	—	—	1	4	22	27	22
Soft drinks	—	1	1	1	5	10	18	14
Egg	—	—	—	—	8	8	16	13
Jello	—	—	—	1	3	7	11	8
Meat, chicken	—	—	—	—	1	2	3	—
Carrots, potatoes	—	—	—	1	—	2	3	—
Honey	—	—	1	—	—	—	1	—

[a] Nine infants were fed both types of milk simultaneously i.e. breast and cow's milk.

baby thrives on it. This belief holds true not only for the young infant, but for some preschool children as well.

Banana was the most preferred fruit. It is considered as suitable for the healthy infant. Oranges and apples were also frequently mentioned by the mothers. Soft drinks were extremely popular especially one called *manzanita* with imitation of apple flavor When children were sick with diarrhea or fever mothers reported a higher consumption of this beverage.

Table 6 shows the number and percentage of infants taking breast milk and other combinations at the end of the first semester of life. Sixty-one per-cent (76 infants) were exclusively breast fed the first trimester of life, while only nine per cent (12 infants) were completely breast-fed at the end of six months. Six per cent of the infants were fed only milk (breast, cow's, goat's milk) during the six months, and twelve per cent were fed *atoles* with milk only The rest of the infants (seventy-three per cent)

Tortilla is fed to children usually mixed with bean soup in order to soften its texture.

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Tortilla	—	—	—	2	10	37	49	39
Bread, crackers	—	—	—	1	9	34	44	35
Sugar	9	6	4	5	7	6	37	30
Chocolate, coffee	3	1	1	3	6	15	29	23
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Egg	—	—	—	—	8	8	16	13
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Cow's milk is given to children almost always boiled, not necessarily for reasons of hygiene, but because unboiled milk is considered to be "cold". For apparently similar reasons, mothers use cinnamon or lime leaves, chocolate and coffee as flavoring agents for the milk. Thus feeding of plain cow's or goat's milk to the child was rarely reported.

By the fourth month most of the twenty-two food items, with the exception of eggs and meats, were already introduced by some mothers.

The broth of the bean soup is usually given to the child, but not the beans as such, as it is believed that they are "heavy" food and that the child cannot tolerate them well. The "goodness" of a food is judged by its digestibility and according to whether or not the

Table 4 *Correlation between infant food scale and infant food scores*

Correlation coefficient 0 70

Food scores	Number of infants in scale steps 1 2	3–4	5–6
Low scores (1–4)	19	16	0
Medium scores (5–8)	7	31	28
High scores (9–12)	1	1	22

Table 5 *Age of introduction by type of food*

Food items	Months 1 (number of infants)	2	3	4	5	6	Total	% of total for row
Breast milk	124	—	—	—	—	—	124	100
Herb teas	96	—	—	1	1	—	98	79
Cow's milk (fresh)[a]	15	6	6	5	5	17	54	43
(powder)[a]	12	6	2	6	1	2	29	23
Goat milk	—	1	—	—	1	1	3	—
Fruit	2	1	3	8	14	25	54	43
Bean soup	—	—	—	4	14	34	52	41
Atoles	13	7	6	7	11	7	51	41
Tortilla	—	—	—	2	10	37	49	39
Bread, crackers	—	—	—	1	9	34	44	35
Sugar	9	6	4	5	7	6	37	30
Chocolate, coffee	3	1	1	3	6	15	29	23
Sopa aguada	—	—	—	1	4	22	27	22
Soft drinks	—	1	1	1	5	10	18	14
Egg	—	—	—	—	8	8	16	13
Jello	—	—	—	1	3	7	11	8
Meat, chicken	—	—	—	—	1	2	3	—
Carrots, potatoes	—	—	—	1	—	2	3	—
Honey	—	—	1	—	—	—	1	—

[a] Nine infants were fed both types of milk simultaneously i.e. breast and cow's milk.

baby thrives on it. This belief holds true not only for the young infant, but for some preschool children as well.

Banana was the most preferred fruit. It is considered as suitable for the healthy infant. Oranges and apples were also frequently mentioned by the mothers. Soft drinks were extremely popular especially one called *manzanita* with imitation of apple flavor. When children were sick with diarrhea or fever mothers reported a higher consumption of this beverage.

Table 6 shows the number and percentage of infants taking breast milk and other combinations at the end of the *first semester of life*. Sixty-one per-cent (76 infants) were exclusively breast-fed the first trimester of life, while only nine per cent (12 infants) were completely breast-fed at the end of six months. Six per cent of the infants were fed only milk (breast, cow's, goat's milk) during the six months, and twelve per cent were fed *atoles* with milk only. The rest of the infants (seventy-three per cent)

Tortilla is fed to children usually mixed with bean soup in order to soften its texture

The fact that the foods in the infant s diet do form a scale is evidence that an underlying pattern exists associated with their feeding habits. It suggests that rather than a merely random list of foods, the food reports collected over a long period are structured quite consistently With the development of the scale, we now also know which individual food groups are included in this dietary pattern.

One implication borne out by the scale is a strong support for the assumption that an infant s dietary pattern does in fact exist in this community On numerous occasions it has been contended that in Latin American rural societies the child is exclusively breast fed during a period of no less than 12–18 months or that no new food is introduced to the child during this period Obviously this is not the case in this village and might not very well be the case for many other Latin American rural areas. Scarcity of empirical quantitative studies to support these contentions have sometimes contributed to some of these over simplified generalizations, particularly in the field of infant nutrition

In a latter section of this discussion we will turn our attention to the relationships obtained between the infant food scale and certain social correlates.

Scoring technique for items that did not scale Due to the fact that some of the food items that were most frequently mentioned by the mothers did not scale a scoring technique was introduced into the analysis to take these foods into account, and later on to correlate them with the infant food scale, so as to introduce a validation factor into the data.

The following six additional food items were considered for scoring.

1 *Atoles* (gruels)
2. Bread, Crackers, Cookies
3 *Sopa Aguada* (watery noodle-like soup)
4 Cocoa or Coffee with Milk
5 Eggs
6 Jello" (flavored gelatin)

Atoles is an item considered suitable fc children which we assumed would scale an which did not. Several scaling attempts wer tried through reshuffling of cases and column In some of these trials atoles was placed l between "Other Milks" and Caldo de Frijol" but the resulting coefficients of scalability wer not acceptable Likewise, *Sopa aguada* customarily served at noon time and also though to be nutritious for children, did not scale Bread and chocolate drinks also reported a frequently consumed by the infants were excluded from the scale because of greater percentage of errors. Eggs were not included because they did not have a very high frequency of use during this early period of the infant s life and so did not scale by themselves, although they did scale in the family food scale to be reported later in this discussion.

The scoring procedure was to assign a score of 1" for each food item present in the infant diet. Twelve food items, six from the scale steps and six from the food list, were included, thus rendering 12 as the maximum possible score that could be obtained by a child. The food scores were trichotomized in the categories of High Scores (9 to 12 items) Medium Scores (5 to 8 items) and Low Scores (1 to 4 items) The results of the correlation between food score and infant s position in the food scale are shown in Table 4

As can be noted in the table, a significant correlation was found between scale and score. Infants having a high score clustered in the higher steps of the food scale, while infants with low scores placed in the lower or medium scale steps. This finding increases the confidence that can be given to the infant food scale as such

(b) *Introduction of foods during the first semester of life*

Table 5 shows a list of twenty-two different food items introduced to this group of infants by the month in which the particular food was introduced. As can be observed from the table there is the widest possible range of foods em-

ployed. In many cases the infants received only small amounts or merely tastes of food, most usually about the age of three to four months.

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Goat's milk	—	1	—	—	1	1	3	—
Fruit	2	1	3	8	14	25	54	43
Bean soup	—	—	—	4	14	34	52	41
Atoles	13	7	6	7	11	7	51	41
Tortilla	—	—	—	2	10	37	49	39
Bread, crackers	—	—	—	1	9	34	44	35
Sugar	9	6	4	5	7	6	37	30
Chocolate, coffee	3	1	1	3	6	15	29	23
Sopa aguada	—	—	—	1	4	22	27	22
Soft drinks	—	1	1	1	5	10	18	14
Egg	—	—	—	—	8	8	16	13
Jello	—	—	—	1	3	7	11	8
Meat, chicken	—	—	—	—	1	2	3	—
Carrots, potatoes	—	—	—	1	—	2	3	—
Honey	—	—	1	—	—	—	1	—

Nine infants were fed both types of milk simultaneously i.e. breast and cow milk.

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Table 6 *Pattern of milk consumption at six month of age*

	No. of Infants	Per centage
Breast milk only[a]	12	9
Breast milk plus cow's milk	8	6
Breast milk plus supplements	31	24
Milk plus *Atoles*	13	1[illegible]
Milk plus supplements	61	49
Total	125	100

[a] At the end of the first trimester 61 of the infants (76 cases) were still fully breast fed.

received either breast milk or cow s milk plus supplements The most common supplements added to this group were *tortillas* bean soup bread or crackers, fruits, *sopa aguada* and eggs.

With respect to the age at which a child can be fully incorporated into the family s diet mother s opinion was divided almost in two halves, with 45% giving 1 to 2 years as the most adequate time and another 46% favoring age two years or more A few mothers (5%) considered that as early as 9 to 11 months is an adequate age Four per cent of the mothers had no opinion as to the best time

3 The Weaning Time

In many areas of the world earlier weaning of infants is becoming more and more common. This has often resulted in increased malnutrition in preindustrial societies since the weaning foods are generally protein deficient. This crucial period in an infant s life has also been associated with increased infant mortality rates and greater incidence of diarrhea.

(a) Maternal beliefs and attitudes on weaning

Whether or not a woman believes she can get pregnant again while lactating may influence, one way or another the length of time she will breast feed the child. In this respect, it is interesting to note that the Mexican mothers in the present sample were divided in their opinion as to the effect of lactation on possible impregnation. Fifty two per cent believed they could conceive while lactating. Twenty two per cent believed they could not get pregnant, and remarked that separation of the child from the breast would indeed mean another pregnancy Fifteen per cent of the mothers were not sure as to the effect. Remarks such as it depends on God s will" "there is not a set rule for this or some women get pregnant while others do not" often came from this last group

A negative correlation was found between the age of the mother and the belief that lactating prevents conception The older the mother the greater the likelihood that she believed or knew through experience that she could conceive while lactating (Table 7)

The mother's attitude toward breast feeding during pregnancy was assessed through the question. should a pregnant woman continue breast feeding her child " Eighty-eight per cent of the mothers responded *no* Ten per cent agreed that they could continue lactation, and 2% did not know what to believe.

Opinions varied as to why a pregnant woman should not give the breast to her child. It seems that most answers bear magical connotations as to the consequences resulting to the child if fed with milk produced during pregnancy It was mentioned for example that children" should not drink this bad" milk

Table 7 *Relationship between belief in lactating as an anticonceptive measure and maternal age*

Correlation coefficient 0.34. Figures in parenthesis represent number of mothers

	Percentage of mothers in age groups (yrs)				
Belief	19	20-23	24-29	>30	
Mother cannot become pregnant during lactation period	19	32	25	13	(27)
Mother can become pregnant during lactation period	38	44	67	61	(69)
Do not know	19	8	3	5	(9)
Are not sure	24	16	5	21	(19)
	(21)	(25)	(39)	(39)	(124)

which is thought to be the product of his mother's sin. Other mothers reported that pregnancy changes the physical properties of the breast milk making it unsuitable for the infant. They claimed that the milk gets thin, yellowish, etc. and therefore, causes diarrhea, vomiting and other stomach ills to the children.

When the responses were cross-tabulated by mother's age, a percentage difference was found to the effect that the younger mothers show less favorable attitudes toward continuing breast-feeding during pregnancy.

With respect to mother's opinion as to the age of introduction of supplementary feeding, 43% favored 3 months or less, another 43% stated 4 to 6 months, while only 13% favored age 7 months or older. No significant relation was found between age of the mother and age of introduction of food supplements. The opinions gathered from the mothers seem to be in agreement with their actual practices. As can be seen in table 5 early introduction of food supplements seem to be the developing trend in this community.

(b) Time of weaning and its association with some variables

The age of the child when the mother refuses the breast is generally between 12 and 18 months as reported by 68% of the mothers. In attempting to find out some explanation for the selection of this time as adequate, correlations between time of weaning and other variables were calculated.

Table 8. *Time of weaning of youngest child as a function of maternal age*

Gamma coefficient 0.37. Significant at 0.05 level. Figures in parenthesis represent number of mothers

Time of weaning (months)	Pregnancy of mothers in age groups (yrs)				
	19	20–23	24–29	30	
18–24	5	8	9	17	(12)
12–18	71	63	77	75	(84)
9–12	4	29	14	8	(20)
	(21)	(23)	(36)	(36)	(116)

Table 9 *Relationship between weaning time and mother's education*

Gamma coefficient = 0.22. Figures in parenthesis represent number of mothers

Weaning time (months)	Mother's education				
	Illiterate	Low	Medium	High	
	Percentage of mothers				
18–24	15	7	7	—	(12)
12–18	77	75	62	86	(84)
9–12	9	18	29	14	(20)
	(47)	(28)	(34)	(7)	(116)

Code for mother's education.
Low = 1–3 years of schooling
Medium = 4–6 years of schooling
High 6 or more years of schooling

Table 8 shows weaning time as a function of maternal age. While for the average time of weaning (1–1 1/2 years) percentage differences do not seem to be affected by mother's age, they do differ considerably at the two extreme weaning brackets with older mothers weaning at later ages.

Table 9 shows the relation between weaning time and mother's education. As can be seen in the table the lower the educational level of the mother (illiterates plus low educated mothers) the greater the likelihood that she will wean at a later time. Conversely the higher the education of the mother the greater the likelihood that she will wean at an earlier time. The degree to which mother's education predicts the weaning period of the child is shown by a gamma coefficient of 0.22.

As could be expected from the association found between mother's age and time of weaning the number of pregnancies also correlated with weaning time. Mothers with a high number of pregnancies were overrepresented in the late weaning group.

Early weaning was significantly associated with place of delivery (Correlation coefficient = 0.37 p less than 0.01). Infants delivered in the hospital falling in significantly higher numbers in the early weaning group. This finding may indicate either the influential effect of the hos-

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Table 10. *Rank correlation matrix for nine indicators of breast feeding practices and social characteristics of mothers (gamma coefficients)*

		2	3	4	5	6	7	8	9
Infant food scale	1	−.09	.06	.01	10	.08	.06	17	−.15
Mother' age	2		−.16	−.14	−.07	−.06	.09	−.06	−.37
Mother education	3			−.03	10	18	.21	−.08	.22
Mother's social orientation	4				.07	.06	−.05	−.34	.01
Attitude toward bottle-feeding	5					.39	.29	.27	15
Type of feeding	6						.31	−.06	.29
Age of supplementary feeding	7							− 10	− 13
Methods of weaning	8								.36
Weaning time	9								

Gamma coefficient significant at the 0.05 level.

pulse, forcing the end of the lactation period. The main reason given for this behavior was the outcome of a new pregnancy

Table 10 shows a rank correlation matrix as a summary of the most relevant variables discussed on breast-feeding practices, and the association with scores on mother's social characteristics.

Upon examination of the correlation matrix, it can be noted that, as expected, mother's age is negatively associated with her educational level. The younger mothers had more years of schooling. Negative association was also found between age and breast feeding practices, to the effect that the higher the mother's age, the lower their ranking on the feeding practices. Similarly social orientation was negatively associated with methods of weaning, to the effect that the traditional-oriented mother was less likely to practice gradual methods of weaning.

In addition, a gamma coefficient of predictability of 0..7 was found for attitude toward bottle feeding versus methods of weaning. The association implies that those mothers who practiced gradual weaning methods also reported a more favorable attitude toward bottle feeding.

Attention is also called to the low degree of association between the infant food scale and the other variables considered.

6 *Food Habits and Folk Medicine*

For a better understanding of the results on food ideology and food habits in certain physiological and pathological conditions, a brief historical reference seems useful in order to place these findings within their proper context.

The present day Latin American folk medicine, in general, has its origins in the indigenous culture that preceded the arrival of the Europeans, and in classical European medicine

The most important single set of ideas governing food related behavior in rural societies of Latin America is a folk manifestation of Ancient Greek humoral pathology modified and developed in the Arab World, diffused to Spain, and transmitted to Spanish America at the time of the conquest (52) In brief, foods, herbs, illnesses, and bodily states are characterized by degree of "hot" and cold" Being important to bear in mind that this hot and cold concept is not related to the food's actual temperature.

A blending of the classical Spanish medical theory with the various indigenous medical beliefs has then resulted in an active folk medicine that exists in both the *Mestizo* and Indian cultures (53). These classical concepts, centuries old, are preserved to a very marked degree in the community and perpetuated through family generations, as part of the natural learning process within that social system (40)

Since hot and cold are innate magic qualities of each food, the outsider does not have any objective criterium for their classification. The female members of the community learn from

pital, or mothers willing to adopt non traditional practices, such as the selection of the hospital instead of the home as the place of delivery

4 Methods of Weaning

The several weaning methods followed by the mothers seem to fall in the following categories

(a) Traditional methods (58 of the cases)

To aid her in freeing the child from the breast the mother has recourse to a number of techniques designed to frighten or repulse Application of bitter substances to the breast is a common practice to discourage suckling. Use of *sábila* a plant whose leaves are bitter was the most frequently reported method Use of charcoal ashes, hot pepper tomato lemon corn dough and garlic applied to the nipples were also mentioned Usually these practices were accompanied by an explanation from the mother telling the infant that the nipple is dirty" or hot" The mothers reported that in most cases one to three applications of these substances were sufficient.

Another traditional method of weaning consists in preventing the child from finding the breast To do this mothers sleep with their clothes on they tie a towel around the breast, or simply avoid sleeping with the child. Geographical separation a usual procedure in other tropical regions was very seldom reported

(b) Sudden weaning (34 of the cases)

Often when a child was suddenly refused the breast it was because the mother discovered she was pregnant again as was mentioned before it is commonly believed that it is harmful for a child to suckle from the breast once the mother has conceived again On other occasions mothers reported that suddenly one day without any special reason they decide not to breast feed the child any more

(c) Up to the child" (13% of the cases)

These mothers seem to be very flexible in their practices, as they reported that they themselves did not do anything to discourage the child from breast feeding, being up to him to refuse the breast. In some cases, the child may have progressed in the eating of semi solid or solid foods to a point where he no longer wants to have breast milk.

(d) Gradual weaning (8% of the cases)

In only eight per cent of the cases the weaning appeared to have been a gradual process, where initiation of bottle feeding and other supplements took place as a preliminary planned stage in preparation for the full separation from the breast.

5 Summary on Weaning Period

A unfavorable attitude toward communal feeding was present in this group. Magical reasons as well as empirical ones were offered by the mothers as the explanation for their behavior

A large majority of the mothers also manifested disagreement with the practice to continue breast feeding if they became pregnant. The reasons given were mainly of a magical nature.

In the sample under study the weaning time is associated with maternal beliefs and attitudes on the contraceptive function of prolonged lactation. The belief that lactating prevents a new pregnancy was more prevalent in the younger mothers. The older mothers claimed that experience" has shown this belief not to be valid

Negative correlations were found between the age of the mother and her education, and the weaning time The younger and better educated mothers were likely to wean at earlier periods.

More than half of the mothers interviewed still practice traditional and sudden methods of weaning the child. They use a variety of traditional techniques designed to frighten or re-

Table 10. *Rank correlation matrix for nine indicators of breast feeding practices and social characteristics of mothers (gamma coefficients)*

		2	3	4	5	6	7	8	9
Infant food scale	1	−.09	.06	.01	.10	.08	.06	.17	−.15
Mother age	2		−16	−.14	−.07	−.06	.09	−.06	−.37
Mother's education	3			−.03	.10	18	.21	−.08	.22
Mother's social orientation	4				.07	.06	−.05	−.34	.01
Attitude toward bottle-feeding	5					.39	.29	.27	.15
Type of feeding	6						.31	−.06	.29
Age of supplementary feeding	7							−.10	−.13
Methods of weaning	8								.36
Weaning time	9								

Gamma coefficient significant at the 0.05 level.

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Table 10 shows a rank correlation matrix as a summary of the most relevant variables discussed on breast-feeding practices, and the association with scores on mother's social characteristics.

Upon examination of the correlation matrix, it can be noted that, as expected, mother's age is negatively associated with her educational level. The younger mothers had more years of schooling. Negative association was also found between age and breast feeding practices, to the effect that the higher the mother's age, the lower their ranking on the feeding practices. Similarly social orientation was negatively associated with methods of weaning, to the effect that the traditional-oriented mother was less likely to practice gradual methods of weaning.

In addition, a gamma coefficient of predictability of 0.27 was found for attitude toward bottle feeding versus methods of weaning. The association implies that those mothers who practiced gradual weaning methods also reported a more favorable attitude toward bottle feeding.

Attention is also called to the low degree of association between the infant food scale and the other variables considered.

6. Food Habits and Folk Medicine

For a better understanding of the results on food ideology and food habits in certain physiological and pathological conditions, a brief historical reference seems useful in order to place these findings within their proper context.

The present day Latin American folk medicine, in general, has its origins in the indigenous culture that preceded the arrival of the Europeans, and in classical European medicine.

The most important single set of ideas governing food related behavior in rural societies of Latin America is a folk manifestation of Ancient Greek humoral pathology modified and developed in the Arab World, diffused to Spain, and transmitted to Spanish America at the time of the conquest (52). In brief, foods, herbs, illnesses, and bodily states are characterized by degree of "hot and cold" Being important to bear in mind that this hot and cold concept is not related to the food's actual temperature.

A blending of the classical Spanish medical theory with the various indigenous medical beliefs has then resulted in an active folk medicine that exists in both the *Mestizo* and Indian cultures (53). These classical concepts, centuries old, are preserved to a very marked degree in the community and perpetuated through family generations, as part of the natural learning process within that social system (40).

Since hot and cold are innate magic qualities of each food, the outsider does not have any objective criterium for their classification. The female members of the community learn from

pital, or mothers willing to adopt non tradi tional practices such as the selection of the hospital instead of the home as the place of delivery

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In addition, a gamma coefficient of predictability of 0..7 was found for attitude toward bottle feeding versus methods of weaning. The association implies that those mothers who practiced gradual weaning methods also reported a more favorable attitude toward bottle-feeding.

Attention is also called to the low degree of association between the *Infant food* scale and the other variables considered.

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Table 11 *Percentage of certain foods permitted and restricted during the post partum and lactation periods*

Food permitted	%	Food restricted	
Soups (chicken broth *sopa aguada*)	86	Avocado	54
Atoles	85	Fruits	50
"Toasted" tortilla	83	Pork meat	43
"Boiled" milk	56	"Red" beans	41
Chicken, beef	50	Vegetables	15
"Black" bean broth	47	"Red" meat	12
"Charcoal broiled" cheese	45	Milk, cheese eggs	17

their elders and peer group the qualification of each food.

In summary foods are intimately involved in the general conception of health and disease and in general almost any degree of illness leads to the withdrawal of part of the food from the child s diet. (3 39)

(a) *Food beliefs as related to pregnancy postpartum and lactation*

During pregnancy mothers reported a regular consumption of their basic diet but this picture is totally reversed once the post partum period arrives.

Table 11 presents the lists of the most common permitted and restricted foods during the post partum and lactation periods

Table 12 shows the relationships between prohibition of foods in several pathological or physiological conditions and mother s age It can be seen from the table the tendency for younger mothers to practice less food restriction. The tendency nevertheless does not reach acceptable levels of significance except for age and restriction in children suffering from measles (gamma coefficient = 0 40; $p <$ 0 05)

The results seem to indicate that in this community there is not a widespread notion of a balanced diet promoting good health in children, but rather the pattern that because the children were healthy" they could afford to eat.

Twenty-eight per cent of mothers reported some prohibition of foods even in healthy children Fruit, avocado, beans and pork meat were mentioned among the most frequently eliminated foods from a healthy child s diet. Children were cautioned not to eat hot pepper or too many thick tortillas since their heat" may cause colic. During the *mango* season, children are warned against excesses of this fruit lest they suffer diarrhea.

Up to 2 years of age protein rich foods, such as meats of any kind, are withdrawn from the diet of a child who develops any signs or symptoms which the mother attributes to the presence of worms.

Food prohibitions were specifically focused during the three most common pathological states in children. Fever diarrhea and measles. While in fever 44% of the cases reported some prohibition of food the percentage increased to 66 in diarrhea reaching a figure of 78% in measles

This attitude again may prevail as a consequence of the beliefs about the relationship of foods conflicting with the disequilibrium of the body rather than in terms of a more scientific knowledge of illness and diet. Thus, pork which is a cold" food even when cooked is

Table 12. *Relationship between food restriction during certain periods and maternal age*[a]

Figures in parentheses represent number of mothers

Restriction of foods	Mother's age (yrs) 19	20–23	24–29	30 +	
In post partum	16	18	4	27	(107)
To healthy children	6	4	9	8	(34)
To sick children in fever	8	7	14	15	(55)
To sick children in diarrhea	10	14	19	22	(82)
To sick children in measles	5	17	26	30	(58)
	(21)	(25)	(39)	(39)	(125)

Gamma coefficients

In post partum	0 16
To healthy children	0.08
In fever	0.07
In diarrhea	0.06
In measles	0.40*

[a] Information has been collapsed from five dichotomized tables, thus, Yes responses are only shown here.
* Significant at the 0.05 level.

Table 13 *Rank correlation matrix on food ideology and social characteristics of the mother (in gamma coefficients)*

		2	3	4	5	6
Age of the mother	1	−0.18	0.16	−0.06	−0.07	0.40*
Educational level of the mother	2		−0.03	0.24	−0.18	−0.49
Food restriction in post-partum	3			−0.18	0.39	1.00
Food restriction in diarrhea	4				0.80	1.00
Food restriction in fever	5					1.00
Food restriction in measles	6					

Significant at 0 05 level.

almost never given to a child suffering from measles, which in turn is considered a "hot" illness. Beef is "hot" thus can be consumed during the post-partum period. Milk is cold" and must be boiled, and cheese must be charcoal broiled over a *comal* (hot plate) before the mother is permitted to consume it after delivery

Table 13 presents a rank correlation matrix *on* food ideology and *some* social characteristics of the mothers.

Upon examination of the multivariate analysis shown in the table, restriction of *foods* during post-partum, diarrhea and fever seem to be powerful predictors of food restriction during measles (perfect positive correlation) In the light of the cultural context in which these practices prevail, it seems logical to assume that if the mother observed food restriction in fever and diarrhea which in her perception are considered minor" illnesses, the likelihood is greater that she will prohibit them in measles, which is *culturally* categorized as a more severe "hot disease. Educational level of the mother shows negative association, to the effect that the medium-higher educated mother had a slight tendency to exercise, *to a lesser degree*, this prolonged or *complete* food restriction.

In general, age of the mother is a poor predictor of *food restriction in all the* situations considered but in measles. A reasonable high gamma coefficient of 0.40 was found to the effect that the older mothers were more likely to observe severe food restriction periods during measles.

Because of the key role played by the mother in determining health behavior and feeding practices of the family Table 14 presents a rank *correlation* matrix on scores of the females included in this sample. A variable presenting each of the broad dimensions studied in this research (health, education, communication, etc.) was selected to be shown in this multivariate analysis.

At this point of the analysis, we would like to bring into the study a second hypothetical *explanation for the* findings presented so far in the section on Food Beliefs, which may theoretically explain the inconsistent trends found in the belief orientation of the mothers.

Reeder (7) theorizes about the specificity" of elements responsible for decision-making and social action. He proposes that the beliefs and disbeliefs of the social actor (mothers) will come from an array of cultural beliefs regarding a specific referent. The social actor as a member of the community society selects one element of the array as his beliefs, letting the non-selected elements become his disbeliefs. In this manner *specific relevant components* regarding the *referent* provide the basis for any decision or *social* action taken by the mothers. *In order to* explain why alternative belief A" is chosen rather than alternative belief "B" it becomes necessary to know these components. The actor Reeder contends, has specific beliefs, attitudes and opinions toward a referent and will react accordingly

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[b] Significant at the 0.05 level.

The last part of our analysis will now focus on a similar attempt, applying correlation methods to the study of food consumption.

1 *The family food scale*. Table 15 shows the family food scale that was obtained from the twenty-four hour food consumption survey The coefficient of scalability of 0 78 is well above the acceptable level.

It can be noted that the first three lower steps of the scale, corn flat bread, beans, hot peppers and tomato form the basis of the diet. Meat and eggs, wheat bread and milk and cheese represent the next three higher steps. Again, as with the infant food scale, the last higher steps appear to be highly selective in the percentage of families eliminated as the diet increases in complexity

The same scoring technique used for the infant food data was applied for those items frequently mentioned but which themselves did not scale. These included six additional items.

1. *Sopa Aguada* (Noodle-like soup)
2. *Atoles* (Gruels)
3. Rice, Potatoes
4. Beverages such as chocolate and coffee
5. Avocado, and other fruits
6. Vegetables

When the family food scale was correlated with the scores, for validation purposes, a high degree of association was obtained (coefficient = 0.80).

As was the case with the infant food scale discussed previously the family food scale presents a pattern in responses, concerning the daily diet, which forms a Guttman scale. It also seems to reflect increasing complexity of food habits. At lower levels, the pattern appears to include relatively few and basic foods. At higher levels, there are more food groups mentioned. This fact lends support to our theoretical contention that food habits and concepts are integrally *involved* in the total framework called "way of life" or complexity of family functioning. If the scale represents a continuum from simple to complex concepts of diet, other simple-to-complex factors of households complexity should show similar trends when compared with the scale.

Table 15. *The family food scale*

Number of cases = 125. Coefficient of scalability = 0.78

Scale steps	Item content	Families %	Families No.
1	Tortilla (corn flat-bread) staple cereal	100	125
2	*Frijoles* (cooked red beans)	98	123
3	Chile *Jitomate* (hot pepper cooking tomatoe)	90	113
4	Meat, eggs	75	95
5	Wheat bread	54	68
6	Milk, cheese	39	49

2. *The food scales and some health and social correlates*. It has been mentioned that the infant food scale appears to be a poor predictor of other levels of functioning of the family Conversely strong support has been found for the family food scale as a reflection of the level of information that the family is processing. This is *evidenced* by contrasting several similar associations (mother's education vs. infant and family food scales) using both variables. One reason for improvement in prediction levels obtained through the family food scale may be that this food scale more meaning-fully reflects a group level operation, i.e. group level analysis, rather than getting at individual attributes, which could be the case of the infant food scale Obviously individual influences operate in both scales (father's and mother's preferences, facilities, perspectives), but in the family food scale these individual attributes are subsumed *to show a reflection of the level of information* within the household.

Certain correlations have been chosen to test some of the theoretical assumptions that if the scales do indeed reflect levels of dietary complexity other differentiation" correlates should also show association with the food scales.

It is customary to treat the diet of the infant under the assumption that each child is an in-

Table 14 *Rank correlation matrix on scores of females (in gamma coefficients)*

		2	3	4	5	6	7
Age	1	−0.18	−0.08	0.46	0.05	0.11	0.17
Educational level	2		*−0.08*	*0.44*	1.00	0.09	0.18
Personal hygiene	3			0.21	0.40	0.55	0.08
Number of pregnancies	4				0.39	0.25	0.33
Reading of newspaper	5					0.35	0.19
Social participation	6						0.10
Social orientation	7						

cial actor will behave differently according to the specific referents.

The data of the present study offers some support for this hypothesis by showing a highly specific nature of food beliefs with regard to the different food prohibitions during sickness periods such as fever measles and diarrhea.

Summary on Section A Maternal and infant nutrition.—Breast feeding practices during the neonatal period show strong attachment to the traditional ways of life although some "modernizing" trends are being felt. Breast milk is still widely acknowledged as the best" milk for a child, mainly for affective reasons, although some practical and economic reasons were also mentioned. Traditional methods are still practiced by the mothers as a way to promote lactation. Among these methods drinking of fluids, specially *atoles* (gruels) and other foods alleged to have specific milk making properties were the most frequently reported by the mothers

An infant food scale with six steps was found, thus evidencing that an underlying pattern exists associated with infant feeding habits in this village.

The introduction of supplementary foods can be summarized by pointing out the fact that a trend for the very early introduction of semi-solids and often their continuation thereafter is evident in this community

The main reasons or rationalizations offered by the mothers to explain their feeding practices and food behavior fell into three categories. magical, empirical and contemporary The meaning of these has been presented in the previous analysis.

The data on maternal beliefs and attitudes on weaning, reveals interesting dichotomies, which in turn suggest dual behaviors Some beliefs and attitudes seem to favor a strong attachment to the traditional ways of life, while others seem to negate it. The data seems to suggest the concept of "specificity" of referents as proposed by Reeder (7) as a helpful theoretical explanatory element in this dualism of social behavior

Food restriction during certain periods such as post partum and lactation, illness in children, etc. were also studied. The magical concept of hot" and cold" as innate properties of foods—regardless of their actual temperature seem to be prevalent in this community as is also the case in some other Latin American communities. This underlying concept also seems to dictate and govern much of the food related behavior observed in this group

A large number of mothers observed food restrictions during the post partum. Eight days was the average number of food restriction days reported during this period. Prohibition of foods to children during fever diarrhea and measles were also reported. This practice was even more severely observed during measles

(b) Food habits and some "differentiation" correlates

Chassy et al (43) have recently reported a Guttman scale (Menzel's coefficient = 0 77) of the food pattern in an industrializing area in Central Mexico This scale indicated not only trends towards increasing complexity of the diet, but correlated as well with other indices of growing modernization patterns

The last part of our analysis will now focus on a similar attempt, applying correlation methods to the study of food consumption.

1 *The family food scale.* Table 15 shows the family food scale that was obtained from the twenty-four hour food consumption survey. The coefficient of scalability of 0.78 is well above the acceptable level.

It can be noted that the first three lower steps of the scale, corn flat bread, beans, hot peppers and tomato form the basis of the diet. Meat and eggs, wheat bread and milk and cheese represent the next three higher steps. Again, as with the infant food scale, the last higher steps appear to be highly selective in the percentage of families eliminated as the diet increases in complexity.

The same scoring technique used for the infant food data was applied for those items frequently mentioned but which themselves did not scale. These included six additional items:

1 *Sopa Aguada* (Noodle-like soup)
2. *Atoles* (Gruels)
3 Rice, Potatoes
4 Beverages such as chocolate and coffee
5 Avocado, and other fruits
6. Vegetables

When the family food scale was correlated with the scores, for validation purposes, a high degree of association was obtained (coefficient = 0.80).

As was the case with the infant food scale discussed previously the family food scale presents a pattern in responses, concerning the daily diet, which forms a Guttman scale. It also seems to reflect increasing complexity of food habits. At lower levels, the pattern appears to include relatively few and basic foods. At higher levels, there are more food groups mentioned. This fact lends support to our theoretical contention that food habits and concepts are integrally involved in the total framework called way of life" or complexity of family functioning. If the scale represents a continuum from simple to complex concepts of

Table 15 The family food scale

Number of cases = 125, Coefficient of scalability = 0.78

Scale steps	Item content	Families %	Families No.
1	Tortilla (corn flat-bread) staple cereal	100	125
2	*Frijoles* (cooked red beans)	98	123
3	*Chile, Jitomate* (hot pepper cooking tomatoes)	90	113
4	Meat, eggs	75	95
5	Wheat bread	54	68
6	Milk, cheese	39	49

diet, other simple-to-complex factors of households complexity should show similar trends when compared with the scale.

2. *The food scales and some health and social correlates.* It has been mentioned that the infant food scale appears to be a poor predictor of other levels of functioning of the family. Conversely strong support has been found for the family food scale as a reflection of the level of information that the family is processing. This is evidenced by contrasting several similar associations (mother's education vs. infant and family food scales) using both variables. One reason for improvement in prediction levels obtained through the family food scale may be that this food scale more meaning-fully reflects a group level operation, i.e. group level analysis, rather than getting at individual attributes, which could be the case of the infant food scale. Obviously individual influences operate in both scales (father's and mother's preferences, facilities, perspectives), but in the family food scale these individual attributes are subsumed to show a reflection of the level of information within the household.

Certain correlations have been chosen to test some of the theoretical assumptions that if the scales do indeed reflect levels of dietary complexity other differentiation" correlates should also show association with the food scales.

It is customary to treat the diet of the infant under the assumption that each child is an in-

Table 14 *Rank correlation matrix on scores of females (in gamma coefficients)*

		2	3	4	5	6	7
Age	1	−0.18	−0.08	0.86	0.05	0.11	0.17
Educational level	2		−0.08	0.44	1.00	0.09	0.18
Personal hygiene	3			0.21	0.40	0.55	0.08
Number of pregnancies	4				0.39	0.25	0.33
Reading of newspaper	5					0.35	0.19
Social participation	6						0.10
Social orientation	7						

cial actor will behave differently according to *the specific referents*

The data of the present study offers some support for this hypothesis by showing a highly specific nature of food beliefs with regard to the different food prohibitions during sickness periods such as fever measles and diarrhea.

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level of association expressed by Kendall's tau was 0.34 for woman's education and 0.29 for man's education (54).

A correlation of 0.20 found for the social orientation of the mother is not as high as was theorized. This is probably due to the fact that a large percentage of the mothers fell into the category of "dual-oriented" which may represent a transitional step where both traditional as well as modern concepts are prevalent in her social orientation. This is a concept hard to measure or tap, since traditional or modern orientation then become a matter of degrees, rather than clear-cut or definite categorizations.

Personal cleanliness of the mother and the presence and proper use of sanitary facilities in the household associated significantly with the family food scale. Gamma coefficients of 0.30 and 0.32 (p less than 0.05) were found, indicating that better levels of hygiene correspond to higher degrees of complexity in the family dietary pattern.

When the professionals who attended the delivery of the youngest infant in the sample were divided into two groups, one formed by the midwives, and the other by medical doctors and nurses trained in obstetrics, a correlation significant at the five per cent level of confidence was found between more sophisticated professional attendant and higher step on the family food scale (gamma coefficient = 0.30)

Length of lactating period of youngest child, by definition, should have been a variable where the structural differentiation concept tested here should have shown trends similar to those found for the food scales, but which did not. The poor correlations found between the scales and the length of the lactating period do not seem to indicate support of the food scales as indexes of "modernizing" attitudes for this particular indicator

Finally with the data available it was decided to test the concept of family differentiation in a much broader context, modeled after Young and Young's (6) study on "The Differentiation of Family Structure in Rural Mexico The variables explored and the coefficients of correlation found are presented in Table 20

Two sets of findings emerge from the examination of the matrix. First, the association of the "complex" households. Even though it is conceded here that the majority of the households in this sample fell into the classification of a relatively homogeneous, traditional "undifferentiated" society the matrix seems to indicate that those households that were indeed "differentiated" seem to cluster on the same complex stream in other diverse activities, especially those indexing the communication variables. And secondly a transitional stage of dualism also seem to be present, as

Table 18. *Relationship between food scale and mother's contact with a mass communication media*

Gamma coefficient = 0.23. Figures in parenthesis represent number of mothers

Infant food scale	Television watching		
	No	Yes	
Steps	*Percentage of mothers*		
1 3 Combined	90	10	(58)
4–6 Combined	85	15	(62)
	(105)	(15)	(120)

Table 19 *Per cent of households in each family food scale step by primary occupation of male head*

Gamma coefficient = 0.35. Figures in parenthesis represent number of households

Family food scale steps	Father's occupation					
	1	2	3	4	5	
1–3 (Combined)	87	—	9	4	—	(23)
4	61	5	10	—	24	(21)
5	61	6	9	—	30	(34)
6	46	19	5	—	30	(37)
	(71)	(16)	(9)	(1)	(24)	(125)

Code for father occupation
1. Agriculture day-laborer (Peon)
2. Owner of family plot (Ejidatario)
3. Land renter (Arrendatario)
4. Small landowner
5. Craftsman or professional

Table 16 *Relationship between the infant food scale and the family food scale (in frequencies)*
Gamma coefficient = 0.16

Infant food scale steps	Family food scale steps 1	2	3	4	5	6	Total
1	—	—	3	3	4	2	12
2	1	1	4	3	1	6	16
3	1	—	6	6	10	10	33
4	—	—	2	2	4	6	14
5	—	—	1	1	2	5	9
6	—	—	6	7	14	14	41
Total	2	1	22	22	35	43	

dependent subject whose food consumption is influenced by factors such as socio-economic status level of the family mother s age and education etc. Since the infant is a member of a social unit it is also assumed that his diet must be influenced by the food availability within the household. Table 16 shows the de gree of association between the infant and the family food scale.

The low gamma coefficient reveals a negligible association This fact, again, lends support to our hypothetical contention that even in the midst of plenty the child is not permitted a full participation of the family s food, for the cultural reasons previously discussed This assumption gets even more support when, as shown in Tables 17 and 18 mother's social participation (measured by her visiting pattern) and mother's contact with the broader culture through the use of media of mass communication, does correlate with the infant food scale Again these findings may indicate broadening and new perspectives for the mother and some support for the scale as a measure of moder nization"

No association of significance was found among family size, mother s education father s education and the infant food scale Of all the father's attributes studied only two father's oc cupation and television watching, correlated significantly with the level of complexity of the infant's diet.

When one turns from the infant to the family food scale another picture is obtained. The number of features of mother s, father's and family circumstances showing statistical significant correlations increases and it is relatively simple to observe that the family food scale taken as a continuum of dietary complexity re flects other complexities found in the group of families studied.

Table 19 shows the occupation of the male head of the household cross-tabulated by the family food scale It may be noticed that day-laborers in agriculture are overrepresented in the low levels of the scale (steps 1 to 3) Crafts men and professionals on the other hand are concentrated in the higher steps. Again attention is called to the fact that in both food scales the relatively high correlations found suggest father s occupation as a strong measure of family s level of complexity

The educational background of the two household heads is also significantly associated with the family food scale It is worth pointing out the fact that the correlation found for the female head (gamma 0 31) is even higher than that of the male head (gamma 0.29) Since education influences the degree to which a per son is exposed to ideas beyond his immediate social milieu, these correlations may indicate that the family food scale is in fact reflecting exposure to other aspects of broader perspec tives.

Chassy has reported similar association for the Mexican communities studied in 1965 The

Table 17 *Per cent of households in each infant food scale step by social participation of female head*
Gamma coefficient = 0.28. Figures in parenthesis represent number of households

Infant food scale	Mother's social participation No (Visiting)	Yes (Visiting)	Total
1–3 (Combined)	34	66	(56)
4–6 (Combined)	18	82	(57)
Total	(29)	(84)	(113)

level of association expressed by Kendall's tau was 0.34 for woman's education and 0.29 for man's education (54).

A correlation of 0.20 found for the social orientation of the mother is not as high as was theorized. This is probably due to the fact that a large percentage of the mothers fell into the category of dual-oriented which may represent a transitional step where both traditional as well as modern concepts are prevalent in her social orientation. This is a concept hard to measure or tap, since traditional or modern orientation then become a matter of degrees, rather than clear-cut or definite categorizations.

Personal cleanliness of the mother and the presence and proper use of sanitary facilities in the household associated significantly with the family food scale. Gamma coefficients of 0.30 and 0.32 (p less than 0.05) were found, indicating that better levels of hygiene correspond to higher degrees of complexity in the family dietary pattern.

When the professionals who attended the delivery of the youngest infant in the sample were divided into two groups, one formed by the midwives, and the other by medical doctors and nurses trained in obstetrics, a correlation significant at the five per cent level of confidence was found between more sophisticated professional attendant and higher step on the family food scale (gamma coefficient = 0.30)

Length of lactating period of youngest child, by definition, should have been a variable

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Infant food scale	Television watching: No	Yes	
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4-6 Combined	85	15	(62)
	(107)	(15)	(120)

Table 19 *Per cent of households in each family food scale step by primary occupation of male head*

Gamma coefficient = 0.35. Figures in parenthesis represent number of households

Family food scale steps	Father's occupation: 1	2	3	4	5	
1 3 (Combined)	87	—	9	4	—	(23)
4	61	5	10	—	24	(21)
5	61	6	9	—	30	(34)
6	46	19	5	—	30	(37)
	(71)	(10)	(9)	(1)	(24)	(125)

Code for father's occupation
1. Agriculture day-laborer (Peon)
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where the structural differentiation concept tested here should have shown trends similar to those found for the food scales, but which did not. The poor correlations found between the scales and the length of the lactating period do not seem to indicate support of the food scales as indexes of "modernizing" attitudes for this particular indicator.

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Two sets of findings emerge from the examination of the matrix. First, the association of the "complex" households. Even though it is conceded here that the majority of the households in this sample fell into the classification of a relatively homogeneous, traditional undifferentiated society the matrix seems to indicate that those households that were indeed differentiated seem to cluster on the same complex stream in other diverse activities, especially those indexing the communication variables. And secondly a transitional stage of dualism also seem to be present, as

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Gamma coefficient = 0.16

Infant food scale steps	Family food scale steps						
	1	2	3	4	5	6	Total
1	—	—	3	3	4	2	12
2	1	1	4	3	1	6	16
3	1	—	6	6	10	10	33
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Total	2	1	22	2.	35	43	

dependent subject, whose food consumption is influenced by factors such as socio-economic status level of the family mother s age and education etc. Since the infant is a member of a social unit it is also assumed that his diet must be influenced by the food availability within the household. Table 16 shows the degree of association between the infant and the family food scale.

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No association of significance was found among family size, mother's education father s education and the infant food scale Of all the father's attributes studied only two father s occupation and television watching, correlated significantly with the level of complexity of the infant's diet.

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Table 19 shows the occupation of the male head of the household cross-tabulated by the family food scale. It may be noticed that day laborers in agriculture are overrepresented in the low levels of the scale (steps 1 to 3) Craftsmen and professionals on the other hand are concentrated in the higher steps. Again, attention is called to the fact that in both food scales the relatively high correlations found suggest father's occupation as a strong measure of family s level of complexity

The educational background of the two household heads is also significantly associated with the family food scale. It is worth pointing out the fact that the correlation found for the female head (gamma 0.31) is even higher than that of the male head (gamma 0 29) Since education influences the degree to which a person is exposed to ideas beyond his immediate social milieu, these correlations may indicate that the family food scale is in fact reflecting exposure to other aspects of broader perspec tives.

Chassy has reported similar association for the Mexican communities studied in 1965 The

Table 17 *Per cent of households in each infant food scale step by social participation of female head*

Gamma coefficient = 0.28. Figures in parenthesis represent number of households

Infant food scale	Mother s social participation		
	No (Visiting)	Yes (Visiting)	Total
1 3 (Combined)	34	66	(56)
4–6 (Combined)	18	82	(57)
Total	(29)	(84)	(113)

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Length of lactating period of youngest child, by definition, should have been a variable

Table 18. Relationship between food scale and mother's contact with a mass communication media

Gamma coefficient 0.21. Figures in parenthesis represent number of mothers

Infant food scale	Television watching: No	Yes	
Steps	*Percentage of mothers*		
1 3 Combined	90	10	(58)
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Family food scale steps	Father's occupation: 1	2	3	4	5	
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	(71)	(10)	(9)	(1)	(24)	(125)

Code for father's occupation

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Gamma coefficient = 0.16

Infant food scale steps	Family food scale steps 1	2	3	4	5	6	Total
1	—	—	3	3	4	2	12
2	1	1	4	3	1	6	16
3	1	—	6	6	10	10	33
4	—	—	2	2	4	6	14
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No association of significance was found among family size, mother's education, father s education and the infant food scale Of all the father's attributes studied only two father's occupation and television watching, correlated significantly with the level of complexity of the infant s diet.

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Table 17 *Per cent of households in each infant food scale step by social participation of female head*

Gamma coefficient = 0.28. Figures in parenthesis represent number of households

Infant food scale	Mother's social participation No (Visiting)	Yes (Visiting)	Total
1–3 (Combined)	34	66	(56)
4–6 (Combined)	18	82	(57)
Total	(29)	(84)	(113)

ther of delivery Similarly no association was found between place of delivery and subsequent food restriction periods during post partum.

Traditional methods and sudden weaning are still the prevalent patterns in this village. The weaning time most commonly reported was from 12 to 23 months, the peak being at 15-18 months. A highly negative significant association was found between mother's age and weaning time of the youngest child. Conversely a positive association was found between mother's educational level and weaning time, to the effect that the better educated female tends to wean earlier Another significant correlation was found between place of delivery and weaning. Having had a child at a hospital increased the likelihood of practicing early weaning.

As expected, mother's age and educational level were negatively associated with many of the breast-feeding practices. The higher the age the lower the ranking on the adequacy of the feeding practices Similarly the older the mother the less the number of years of schooling completed. However the age relationship did not always hold throughout some of the variables tested. In the case of food prohibitions during the post partum period, or when the child was sick with measles, age did not seem to make any difference and both attributes operated independent of each other These findings lend support to the contentions outlined in our multicaused model, in the sense that these traditional beliefs on how to feed the infant are so deeply imbedded in the culture, in such a pervasive way that they appear to function somewhat independent of many other social factors.

These particular data also lend support to the concept of "specificity" of elements of decision-making and social action, as outlined by Reeder (7), who has suggested that the individual tends to choose his beliefs and disbeliefs from an array of cultural elements. Accordingly his social behavior will be specific rather than general.

The responses concerning the infant and family food data form two six-step Guttman scales. This is considered one of the relevant findings of the study since the development of both food scales shows that there is indeed an underlying structural pattern of food behavior in the community

The infant food scale showed negligible association with most of the variables. Exceptions were father's occupation and mother's social participation which gave significant levels of correlation.

The family food pattern correlates well with some indicators of social position, education and communication variables, both for male and female heads of the households.

The food pattern also correlates well with some indicators of modern health practices, while at the same time yielding negligible correlations with others such as the length of the lactation period. This was especially true of the family food scale, which appeared to be a better predictor of the differentiation correlates.

Of all the social characteristics studied, mother's education proved to be the variable strongly associated with the family food scale. This, again, reiterates the important role of women's education as a key factor in planning and implementing health programs.

Taking the two food scales and the length of the lactation period as the three main behavioral variables of the study it becomes relatively simple to compare their correlation values and to derive from the findings the notion of their independence, as evidenced by their lack of association (gamma coefficients of 0.16, 0.11 and 0.10) respectively for family food scale versus infant food scale, length of lactating period versus infant food scale, and length of lactating period versus family food scale.

Three main questions were posed at the beginning of the study What were the actual infant feeding practices and weaning habits, what were the reasons or rationalizations behind them (beliefs, attitudes, food ideology etc.) and what were the social characteristics of the

Table 20 *Rank correlation matrix on scores of family functions (in gamma coefficients)*

		2	3	4	5	6	7	8	9	10	11	12	13	14
Infant food scale	1	16	11	.06	.28	.01	08	19	.23	.08	.24	.03	.07	.33
Family food scale	2		10	.31	.07	.20	.23	.27	.26	.29	.35	42	12	.05
Weaning time	3			.22	.30	.01	11	.02	13	.20	06	43	−.06	19
Mother's education	4				− 01	.07	77	.22	49	44	47	.36	17	.34
Mother s social participation	5					07	−.35	− 01	− 06	.24	.24	− 05	10	.23
Mother's social orientation	6						− 10	.07	.68	.23	.32	.20	16	.28
Mother's reading newspaper	7							65	.58	44	.33*	.58	.51	.50
Mother s listening to radio	8								82	11	.28*	17	99	.69*
Mother's watching T V	9									61	.05	65	1.00	.98
Father s education	10										.27	.82	.04	.34
Father's occupation	11											.29	.25	.05
Father's reading newspaper	12												.42	*
Father's listening to radio	13													.85
Father's watching T V	14													

Significant at the 0.05 level (one-tailed test).
1 60 or better where level of significance at 0.05 level (one tail) – 1 645
* Due to an error in computer programming, this information was not available for this cell.

exemplified by the fact that neither the infant food scale nor the length of the lactating period of youngest child followed this complexity continuum. This dualism could be taken as evidence that families may be differentiated for some activities and undifferentiated for some others This pattern would offer additional support to the Specificity" concept in social action, rather than to a generalized set of family behavior

It is felt that, if upon further testing, the theoretical contentions underlying the specificity concept are proven valid the model could make a significant contribution to the rationality of health and nutrition education programs

OVERVIEW

The overall findings of the present study seem to support the conclusion that poor feeding practices and weaning habits during the first six months of life are associated with some of the general familial, social and cultural factors that have been proposed as characteristic of the areas where malnutrition in young children is prevalent (55)

The pre scientific conceptions are one of the main determinants of the infant feeding in the community These primitive concepts of food, health and disease, in turn influence the pattern of distribution of available food within the family giving as a net result a reduction in the type and amounts of food that lactating women, infants and pre-school children are allowed to consume The lack of correlation between the family food availability and the infant food intake as well as the beliefs statements about foods offered by the mothers, seem to support this conception.

A trend for the early introduction of feeding supplements is evident. At the end of the first trimester 61% of the infants were fully breast-fed, and only 9% of these continued with this practice at the end of the first semester of life. This finding is dramatic in the light of a previous study (32) reporting 91% of the infants fully breast fed at the end of the first six months in the same village just a few years ago Moreover in the present study it is to be noted that 20 of the 22 food items reported as introduced during the first six months were already being given by the end of the fourth month of life

An association was found between place of delivery and type of feeding practices, to the effect that having a child delivered at a hospital increased the likelihood of rigid scheduled feeding. No association was found between the family's socio-economic status and choice of

place of delivery Similarly no association was found between place of delivery and subsequent food restriction periods *during post-partum*.

Traditional methods and sudden weaning are still the prevalent patterns in this village. The weaning time most commonly reported was from 12 to 23 months, the peak being at 15-18 months. A highly negative significant association was found between mother's age and weaning time of the youngest child. Conversely a positive association was found between mother's educational level and weaning time, to the effect that the better educated female tends to wean earlier Another significant correlation was found between place of delivery and weaning. Having had a child at a hospital increased the likelihood of practicing early weaning.

As expected, mother's age and educational level were negatively associated with many of the breast-feeding practices. The higher the age the lower the ranking on the adequacy of the feeding practices. Similarly the older the mother the less the number of years of schooling completed. However the age relationship did not always hold throughout some of the variables tested In the case of food prohibitions during the post-partum period, or when the child was sick with measles, age did not seem to make any difference and both attributes operated independent of each other These findings lend support to the contentions outlined in our multicaused model, in the sense that these traditional beliefs on how to feed the infant are so deeply imbedded in the culture, in such a pervasive way that they appear to function somewhat independent of many other social factors.

These particular data also lend support to the concept of specificity of elements of decision-making and social action, as outlined by Reeder (7), who has suggested that the individual tends to choose his beliefs and disbeliefs from an array of cultural elements. Accordingly his social behavior will be specific rather than general.

The responses concerning the infant and family food data form two six-step Guttman scales. This is considered one of the *relevant* findings of the study since the development of both food scales shows that there is indeed an underlying structural pattern of food behavior in the community

The infant food scale showed negligible association with most of the variables. Exceptions were father's occupation and mother's social participation which gave significant levels of correlation.

The family food pattern correlates well with some indicators of social position, education and communication variables, both for male and female heads of the households.

The food pattern also correlates well with some indicators of modern health practices, while at the same time yielding negligible correlations with others, such as the length of the lactation period. This was especially true of the family food scale, which appeared to be a better predictor of the differentiation correlates.

Of all the social characteristics studied, mother's education proved to be the variable strongly associated with the family food scale. This, again, reiterates the important role of women's education as a key factor in planning and implementing health programs

Taking the two food scales and the length of the lactation period as the three main behavioral variables of the study it becomes relatively simple to compare their correlation values and to derive from the findings the *notion* of their independence, as evidenced by their lack of association (gamma coefficients of 0 16, 0.11 and 0 10) respectively for family food scale versus infant food scale, length of lactating period versus infant food scale, and length of lactating period versus family food scale.

Three main questions were posed at the beginning of the study What were the actual infant feeding practices and weaning habits, what were the reasons or rationalizations behind them (beliefs, attitudes, food ideology etc.) and what were the social characteristics of the

Table 20 *Rank correlation matrix on scores of family functions (in gamma coefficients)*

		2	3	4	5	6	7	8	9	10	11	12	13	14
Infant food scale	1	16	11	.06	.28	01	08	19	.23	.08	.24	.03	.07	.33
Family food scale	2		10	.31	.07	.20	.23	.27	.26	.29	.35	42	12	.05
Weaning time	3			.22	.30	.01	11	.02	13	.20	.06	.43	−.06	19
Mother's education	4				−.01	.07	77	.22	49	44	47	.36	17	.34
Mother's social participation	5					.07	−.35	−.01	−.06	.24	.24	−.05	10	.23
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The findings of the present study support the hypothesis that the characteristics of typical familial complex of preindustrial societies, seems to be the underlying phenomenon of malnutrition problems in those areas: large families, high parity low levels of education, minimal contact with contemporary knowledge through mass communication media and health personnel, and a strong attachment to the traditional ways of life.

The findings of the study also support the conclusion that breast-feeding practices and weaning habits during the first six months of life are strongly associated with these general familial, social and cultural factors.

Early introduction of feeding supplements, a trend toward lessening the breast feeding period, as well as attitudes concerning acceptance of bottle-feeding practices were found.

Pre-scientific conceptions of food, health and disease held by the majority of the women studied strongly influence and still determine the feeding patterns. Severe food restrictions during healthy and sick stages imposed on children and lactating women seem to confirm the above consideration.

A significant negative association was found between mother's age and length of lactating period of the youngest child, with older mothers weaning at later periods. Similarly negative correlations were found with many of the breast feeding practices and mother's age and educational level.

Two six-step Guttman scales for the infant and family food consumption data were found with high coefficients of reproducibility

The family food scale theorized as indicator of dietary complexity correlated well with other indicators of complexity in the family's way of life" The infant food scale departed completely in this sense, indicating a dualism which supports Reeder's concept of specificity of elements of decision making and social action. Associations were found between the family food scale and social position, education and communication variables, as well as with indicators of modern" health practices.

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The infant feeding practices reported confirm the assumption that in a preindustrial *community in the transition period* a large number of children are given solids during the first six months of life, and that artificial feeding of a complementary nature is quite common in this community As to the rationalizations behind feeding habits it was found that they mainly fell into three categories. magical reasons, involving primitive or pre scientific concepts of food and disease empirical reasons in which mothers suggested practical explanation without the causative relationship concept and contemporary reasons whereby the mothers linked their food behavior to some "modern" concept and attitude

Speculations were also formulated with regard to the nature of mechanisms through which the social characteristics of the mother influence the feeding habits of her children. Her age, educational level social participation and social orientation were studied at length through cross-tabulation and multivariate analysis methods Except for mother's education no other consistent pattern of the social characteristics was found associated with infant feeding practices. The more education she had the more modernizing practices she used and conversely the less her education the more traditional practices she employed. Due to the small percentage (7%) of high" educated mothers within the group it would be convenient to study a more modern community trying to find out a probable ceiling. It may be remembered that growth achievement in length, as well as body weight gain in two separate studies were found to be highly correlated with mother s education (41) (55)

With respect to the main hypothesis that family s as well as infant s food intake patterns would be similarly associated with selected family characteristics, it was found that the selected family characteristics were much more related to the family food scale than to the infant food scale. In fact, it was found that families reacted differently to infant feeding as compared with family feeding. And it was also found that these two were not significantly associated with each other It was further found that some communication variables were significantly associated for both scales, but the communication sources relevant to the infant food scale were different than for the family food scale

All the data are consistent with the idea that the infant is treated by the family with a different set of rules, attitudes and beliefs. As he grows older more and more incorporation into the family as a unit occurs. Infant feeding finally becomes that of the family and the complexity of the diet then reflects the complexity of the "way of life"

It has been emphasized throughout the research analysis that the importance of considering the nutrition problem in rural societies is not as a pure health or dietetic issue, but rather that malnutrition is viewed as a breaking point produced by the convergence of multiple factors and stresses If meaningful nutrition programs are to be implemented, carefully planted strategies" relating to such features as local ecology cultural attitudes and concepts in relation to particular foods and illnesses, level of agricultural technology health problems and their associated conditioning factors must all be considered and must always be appreciated and investigated prior to the planning and implementation of such projects Until and unless interventionists" in developing regions realize that some basic and meaningful field research is needed as a preliminary step before attempting to solve these problems, optimum use of inputs and human resource will be hard to achieve.

SUMMARY

The major purpose of this study was to assess the infant feeding pattern and weaning habits

in a group of 125 infants in relation to their mothers social characteristics and other presumably related background factors. Specific objectives included the utilization of research methods and techniques of social science in the field of nutrition and the exploration of traditional feeding practices and food ideology within a cultural context.

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The findings of the study also support the conclusion that breast-feeding practices and weaning habits during the first six months of life are strongly associated with these general familial, social and cultural factors.

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APPENDIX A INSTRUMENTS

(English Formats)

Form 1 A *Background data*

Date ______________________ Family no. ______________

Family Identification

1 Name of head of the family ______________________
Principal occupation ______________________
a) Farmer: Small landowner Farm laborer Guaranteed holding
b) Worker: Craftsman Merchant Professional
c) Unemployed

2. Address Place of burth

3 Place of birth of child's grandfather (paternal line)
Place of residence Age

4 Place of first employment (head of the family)
Starting age
Former place of work and duration
Initial date of residence in the village

5 Size of household

Adults

Sex	18 to 40 yrs. old	41 to 60 yrs. old	61 yrs.	Total
Male				
Female				
Total				

Children

Sex	0 to 1 month	1 to 11 months	1 to 2.5 years	2.5 to 7 yrs.	7 to 12 yrs.	12 to 18 yrs.	Total
Male							
Female							
Total							

6. Size of nuclear family (head, spouse and children)
Number of relatives
Number of attached individuals
Number of servants

7 Number of contributing wage earners
Number of non-contributing wage earners
Number of unpaid workers (apprentices)
Number of members unemployed

8. Religion

9 Civil status

10. Place of birth of grandmother (maternal line)
Place of residence Age

Form 1-B *Family composition and occupation*

Date ______________________ Family No. ______________

	Classif	Name	Age	Men Children	Adults	Women Children	Adults	Occupation	Agriculture: Small landowner	Guaranteed land-holding	Arrendatario (rents land)	Agricultural laborer	Others: Businessman	Professional	Unemployed	Schoolchildren
Head of household																
Wife																
Children																
Relatives																
Attached individuals																
Servants																
Total																

Form 1.3 *Housing conditions*

Family no. ______

Orientation of entrance

Constructed of Walls ______

Roof ______ Floor ______ Doors ______

Windows ______ No. of rooms ______ No. of windows per room ______

Free space ______

Facilities

Water: Pipes ______ Drinkable ______ Well ______

River ______ Community faucet ______

Inside plumbing ______

Electrification

Light ______ Other services ______

Gas: Stove ______ Refrigerator ______

Other fuels used ______

Purpose ______

Toilet

Location ______

Type

On the ground ______ Buried ______ Latrine ______

With running water ______ Septic tank ______

Water closet. With running water ______ Without running water ______

Bath

Location ______ Type ______ Drainage ______

Bedrooms: No. ______ No. of persons per room ______

Adults Males Females

Children Males Females

Ventilation ______

Kitchen: Location ______

Description ______

Garbage disposal. Location

Description

Animals in house ______ Which ones ______

Special animal quarters

How is manure handled

Presence of ectoparasites

Sanitary nuisances.

Smoke ______ Dust ______ Insects ______ Garbage ______

Family gathering place ______

Form 1 A. *Background data*

Date ____________________ Family no. ____________

Family identification

1 Name of head of the family ____________________
Principal occupation ____________________
a) Farmer: Small landowner Farm laborer Guaranteed holding
b) Worker: Craftsman Merchant Professional
c) Unemployed

2. Address Place of birth

3 Place of birth of child's grandfather (paternal line)
Place of residence Age

4 Place of first employment (head of the family)
Starting age
Former place of work and duration
Initial date of residence in the village

5 Size of household

Adults

Sex	18 to 40 yrs. old	41 to 60 yrs. old	61 yrs. +	Total
Male				
Female				
Total				

Children

Sex	0 to 1 month	1 to 11 months	1 to 2.5 years	2.5 to 7 yrs.	7 to 12 yrs.	12 to 18 yrs.	Total
Male							
Female							
Total							

6. Size of nuclear family (head, spouse and children)
Number of relatives
Number of attached individuals
Number of servants

7 Number of contributing wage earners
Number of non-contributing wage earners
Number of unpaid workers (apprentices)
Number of members unemployed

8. Religion

9 Civil status

10. Place of birth of grandmother (maternal line)
Place of residence Age

Form 1-B *Family composition and occupation*

Date ____________________ Family No. ____________

	Classif.	Name	Age	Men Children	Adults	Women Children	Adults	*Occupation* Agriculture: Small landowner	Guaranteed land-holding	Arrendatario (rents land)	Agricultural laborer	Others: Businessman	Professional	Unemployed	Schoolchildren
Head of house-hold															
Wife															
Children															
Relatives															
Attached individuals															
Servants															
Total															

Form 1.5 *Personal hygiene*

Family no. ____________

Date ____________________ Time ____________________

1. *Hair*
   - 1.1 Clean
   - 1.2 Combed
   - 1.3 Infection
   - 1.4 Parasites

2. *Face*
   - 2.1 Clean
   - 2.2 Infection
   - 2.3 Parasites

3. *Hands*
   - 3.1 Clean
   - 3.2 Infection
   - 3.3 Parasites

4. *Hand Nails*
   - 4.1 Clean
   - 4.2 Cut
   - 4.3 Infection
   - 4.4 Parasites

5. Feet
   - 5.1 Clean
   - 5.2 Infection
   - 5.3 Parasites

6. *Shoes*
   - 6.1 Sporadic use
   - 6.2 Occupational use
   - 6.3 Constant use
   - 6.4 State of repair
   - 6.5 Cleanliness

7. *Bathing*
   - 7.1 Frequency
   - 7.2 Method
   - 7.3 Change of underclothes
   - 7.4 Change of clothes

8. *Clothes*
   - 8.1 Fully clothed
   - 8.2 State of repair
   - 8.3 Cleanliness
   - 8.4 Parasites

Observations: (old or new dirt) ____________________

(derived from work) ____________________

Form 1 4 *Instructions for the recording of minimal conditions for sanitary conditions of dwellings*

Family no. ____________

If all criteria are met, mark the item as positive. With one or more criteria failing, mark the item as negative.

1 General.
- 1 1 Cleanliness made of materials that are cleanable and are kept clean.
- 1.2 *Floors* waterproof smooth, and clean.
- 1.3 Walls full, smooth, impermeable in rooms of water usage (kitchen, bathroom, toilet).
- 1 4 Roof full and impermeable.
- 1.5 Ventilation efficient and constant in bathroom and kitchen.
- 1 6 Degree of sunlight, bedrooms and living room oriented toward south, east or west, or brightly lighted toward north.
- 1 7 Daytime illumination. all areas with light level adequate for easy reading.
- 1.8 Illumination at night One outlet for each separate area of the house.

2. Facilities for personal Hygiene.
- 2.1 Elimination water closet or equivalent for each family
- 2.2 Bath, an adequate washing place.
- 2.3 Hand Washing: an adequate facility
- 2.4 Washing kitchen utensils, a sink.
- 2.5 Washing of clothes a wash tub.
- 2.6 Water adequate supply and draininage for each of the above.
- 2.7 Eating facilities. a table and a chair for each member dining.
- 2.8 Kitchen separate with a stove at least 70 cms. from floor
- 2.9 Sleeping accomodations. any type of bed in places other than the kitchen and bathroom.

3. Conditions of crowding and exposure.
- 3 1 Parents isolated or with children under 3 years of age. Six cubic meters of ventilation per person.
- 3.2 *Children both sexes Five m^3 of ventilation per person.*
- 3.3 Adults separation of sexes six m^3 of ventilation per person.
- 3.4 Animals, should not live in house. Free entrance should not be permitted.

4. Storage facilities.
- 4 1 Clothes, utensils and tools should have adequate places.
- 4.2 Workshop store, animal house are allowed if they do not produce noise or bothersome odors, or represent a danger When other persons are involved in the work they should be isolated from the dwelling and have direct access to the street.

5 Nuisances.
- 5 1 Smoke, dust, insects, pests, poisonous animals and other animals should not exist.
- 5.2 Kitchen waste adequate place of storage.
- 5.3 Refuse adequate place of storage.

Form 1.5 *Personal hygiene*

Family no. ______________

Date ______________ Time ______________

1. *Hair*
   - 1.1 Clean
   - 1.2 Combed
   - 1.3 Infection
   - 1.4 Parasites

2. *Face*
   - 2.1 Clean
   - 2.2 Infection
   - 2.3 Parasites

3. *Hands*
   - 3.1 Clean
   - 3.2 Infection
   - 3.3 Parasites

4. *Hand Nails*
   - 4.1 Clean
   - 4.2 Cut
   - 4.3 Infection
   - 4.4 Parasites

5. *Feet*
   - 5.1 Clean
   - 5.2 Infection
   - 5.3 Parasites

6. *Shoes*
   - 6.1 Sporadic use
   - 6.2 Occupational use
   - 6.3 Constant use
   - 6.4 State of repair
   - 6.5 Cleanliness

7. *Bathing*
   - 7.1 Frequency
   - 7.2 Method
   - 7.3 Change of underclothes
   - 7.4 Change of clothes

8. *Clothes*
   - 8.1 Fully clothed
   - 8.2 State of repair
   - 8.3 Cleanliness
   - 8.4 Parasites

Observations: (old or new dirt) ______________

(derived from work) ______________

Form 1 4 *Instructions for the recording of minimal conditions for sanitary conditions of dwellings*

Family no. ______________

If all criteria are met, mark the item as positive. With one or more criteria failing, mark the item as negative.

1 General.
- 1 1 Cleanliness made of materials that are cleanable and are kept clean.
- 1.2 Floors waterproof smooth, and clean.
- 1.3 Walls. full, smooth, impermeable in rooms of water usage (kitchen, bathroom, toilet).
- 1 4 Roof full and impermeable.
- 1.5 Ventilation efficient and constant in bathroom and kitchen.
- 1 6 Degree of sunlight. bedrooms and living room oriented toward south, east or west, or brightly lighted toward north.
- 1 7 Daytime illumination all areas with light level adequate for easy reading.
- 1 8 Illumination at night. One outlet for each separate area of the house.

2. Facilities for personal Hygiene.
- 2.1 Elimination water closet or equivalent for each family
- 2.2 Bath. an adequate washing place.
- 2.3 Hand Washing: an adequate facility
- 2.4 Washing kitchen utensils. a sink.
- 2.5 Washing of clothes. a wash tub.
- 2.6 Water adequate supply and draininage for each of the above.
- 2.7 Eating facilities a table and a chair for each member dining.
- 2.8 Kitchen separate with a stove at least 70 cms. from floor
- 2.9 Sleeping accomodations. any type of bed in places other than the kitchen and bathroom.

3. Conditions of crowding and exposure.
- 3.1 Parents isolated or with children under 3 years of age. Six cubic meters of ventilation per person.
- 3.2 Children. both sexes. Five m^3 of ventilation per person.
- 3.3 Adults. separation of sexes, six m^3 of ventilation per person.
- 3 4 Animals should not live in house. Free entrance should not be permitted.

4. Storage facilities.
- 4.1 Clothes, utensils and tools should have adequate places.
- 4.2 Workshop, store, animal house are allowed if they do not produce noise or bothersome odors, or represent a danger When other persons are involved in the work they should be isolated from the dwelling and have direct access to the street.

5 Nuisances.
- 5 1 Smoke, dust, insects, pests, poisonous animals and other animals should not exist.
- 5.2 Kitchen waste adequate place of storage.
- 5.3 Refuse adequate place of storage.

Form 1.7 *Visiting form*

Family no. ____________

Date of visit ______________________

Hour ______________________

1. Were there any visits found in the house?

2. Who? Name: ______________________

   Relatives ______________________

   Friend ______________________

   Neighbour ______________________

   Godmother ______________________

   Midwife ______________________

   Others ______________________

3. Where does the visitor live?

   In town ______________________

   Outside town ______________________

4. Time spent on the visit ______________________

5. Purpose of the visit ______________________

____

6. Members of the family who are visiting today ______________________

   Whom are they visiting? ______________________

   Purpose of their visit ______________________

____

Form 1 6. *Literacy and use of printed information*

Knows how to read
Where learned
Completed grades
- Kindergarten
- Spanish
- Elementary
- Junior High School
- Senior High School
- Professional
  - Completed
  - Uncompleted

Current grade

Read newspapers daily ______ Some special section ______

Magazines ______ Which ones ______

How often ______ Reads novels or other books ______

What types ______

How often ______ Reads some technical information related to his or her work ______ Which ones ______

Who provides him or her with the technical information ______

Does he or she believe this reading is helpful to him (her) ______

Use of other communication media

Radio.

1 Do they have a radio at home? ______ What type? ______
2. Do they listen to the radio? ______ Where? ______
3 At what time? ______ 4 What days? ______
5 What programs do they listen to? ______
6. What do they like most? ______
7 Who selects the programs? ______

Television.

1 Do they have a T V set? ______
2. Do they look at television? ______ Where? ______
3 At what time? ______
4 What days? ______
5 What programs do they watch? ______
6. What do they like most? ______
7 Who selects the programs? ______

Form 3.00 *Nutrition questionnaire*

Form 3.1 Concepts and attitudes toward food.

1. What is food?
2. What is food for?
3. How many types of foods there are?
4. Which do you think are the principal foods?
5. Who should eat them?
6. Why should o eat?
7. What do the foods give to the body?

Form 3.2. Which food groups do you know?

I. 1 Milk ________ Cheese ________ Cream ________
2. Meat ________ Poultry ________ Fish ________
Seafood ________ Reptiles ________ Eggs ________

II. 3 Green and yellow egetables
4. Citrus and other fruits
5. Potatoes and other roots
6. Bread, tortillas, cereals and others
7. Butter and other fats

Form 3.3 Techniques of food preparation and preservation.

1. Who prepares the meals?
2. Where?
3. With what? (utensils used, kitchen equipment, etc.)
4. How? (boiled, baked, fried, etc.)
5. Personal hygiene of the person who prepares the meals, water used.
6. Food Preservation (how where, time, etc.)
7. How are any special foods prepared? (during disease periods)

Form 3.4. Child's feeding pattern from birth to weaning.

1. What food is given to the child at birth?
2. Why that food and not other?
3. How is it prepared?
4. How is it given?
5. How many times day? How many days
6. Who recommended to you that food?
7. When, after birth, do you feed him for the first time?
8. Why at that particular time
9. What do you do so that your child can accept the breast?
10. Should the mother alway breastfeed her child?
Why yes ______ Why not ______
11. If the mother cannot breastfeed her child, can other woman do it?
Why yes ______ Why not ______
If yes, ho could that woman be? (relative, friend, stranger etc.)
12. How long does woman has breast milk?
13. If the mother has enough milk, but does not lactate her child, does anything happen to her? To her child? Why? ______
14. If you were proposed to bottle feed your child, would you accept it? Why yes ______ Why not? ______
15. If mother does not have enough milk to lactate her child, what can she do to promote lactation?
16. If she does not hav milk, thus cannot breast feed, what food would you think is the best to give the child? Why ______
17. If she cannot get that food, what other food could she give him?
18. If the mother is breastfeeding her child, is she protecting herself against another pregnancy? Why yes ______ Why not ______
19. Should pregnant woman continue to breastfeed her child? Why yes ______ Why not ______
20. What does it mean to you to practice breastfeeding?
21. Do you enjoy breast feeding your child? Why yes ______ Why not ______
22. What schedule do you follow in lactating your child?
23. In each breast feeding, do you feed him from both breasts? Why?
24. Position used in lactation: Lying down ______ Sitting ______ Why?
25. Do you feed him in any special place in the house? Where? Why?
26. What care should the mother take with her breasts? Why?
27. At what age should the child be fed another food besides breast milk? Which food? Advantages of that food? Why that food and not others. Who recommended it? Quantity? Time? How is it given? Who prepares it?
28. What other food is given or introduced later? Age?
29. What other food is given next? Repeat questions as many times as it is necessary based on the new foods introduced.

Hospital Infantil de Mexico

Rural Research Center

Daily infant food intake

Form 5.2
(pages 1 & 2)

Name of the mother ____________
Name of the child ____________
Key ____________
Healthy (________) Sick (____________)
Name of disease ____________

Date of birth ____________
Age in _____ Weeks _______
Days _____ Cms. _______
Date of the study ________

Date	*Food*	Quantity each time	Feeding schedule	Quantity each day	Food composition			Method of preparation	Food hygiene
					Ingredients	Quantity household measure	Weight in gms.		

New foods introduced during the period that is being recorded				Foods that child continues to eat even though was not consumed the day survey was taken	Foods withdrawn from the child's diet during the period that is being recorded		Observations
Name of food	Date of introduction	Number of times it has been consumed	Quantity each time		Name of food	Why	

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28. What other food is given or introduced later? Age?
29. What other food is given next? Repeat questions as many times as it is necessary based on the new foods introduced.

30 Until what age is mother s milk good for the child? Why?
31 Methods of weaning.
32. At what age is the child weaned? Why at that age?
33 What other foods should be given instead of mother's milk?
34 What other foods should be given next? Who recommended it?
35 At what age should a child be fed like the rest of his family Why at that age?
36. Is the same feeding pattern followed for boys as for girls? Why yes ________ Why not ________

Form 3.5 Foods that healthy persons should eat.

1 In your opinion, which are the foods for adults? Why?
2. For children 1 to 3 years old? Why?
3 For children 3 to 6 years old? Why?
4 For children 6 to 12 years old? Why?
5 For adolescents? Why?
6. For pregnant women? Why
7 For puerperas? Why?
8. For lactating women? Why?

Form 3.6 Foods that healthy persons should not eat.

1 In your opinion, which are the foods that healthy adults should not eat? Why?
2 7 — Repeat the same questions just varying the individual, as was done in form 3.5

Form 3 7 Foods that should be eaten by sick persons.

1 In your opinion, what should a child sick with diarrhea eat? Why
2 A child with fever? Why
3 A child with measles Why?
4 A child with other diseases? Why?
5 An adult with diarrhea? Why?
6. An adult with fever? Why?
7 An adult with other diseases? Why

Form 3.8 Foods that should not be eaten by sick persons.

1 In your opinion, what should a child sick with diarrhea not eat? Why?
7 Repeat the questions, as done in Form 3.7

Form 3 9 Family food consumption survey

Enumerate all the foods consumed by the family the day before List the foods, names, quantities, time by the three main meals of the day

Breakfast *Lunch* *Supper*

Who distributes the foods Who makes the decision as to what foods to buy and consume?

Form 3 10 Nutritional aspirations of the housewife.

1 When you do have some extra money what foods do you buy? Why?
2 What foods you think should not be missing from your meals? Why
3 If you would have more money what foods would you buy? Why?

Form 3 11 Mother's education.

1 Did you go to school? Yes ____ No ____ Last grade completed ______
2 Have you attended any adult education classes? Yes ______ No ______
3 If yes, what types of classes were they? ____________
4 Any other type of informal education?
5 Did you study any home economics courses at school? Yes ______ No ______
If yes, for how long Areas Sewing ______ Cooking ______ Child Care ______
6. Did you study any first aid courses? Yes No ______ *How long* ______
7 10. Her father's and mother's education ______ ______
11 12. Her father s and mother s occupation ______________